The Journal of Pediatrics

VOL. 28 APRIL, 1946 NO. 4

Original Communications

ISOLATION OF ST. LOUIS ENCEPHALITIS VIRUS FROM THE PERIPHERAL BLOOD OF A HUMAN SUBJECT

RUSSELL J. BLATTNER, M.D., AND FLORENCE M. HEYS, PH.D.
ST. LOUIS, MO.

IN SO far as we are aware, virusemia in St. Louis encephalitis has not been demonstrated in the human subject. Under experimental conditions in animals, however, virusemia with the virus of St. Louis encephalitis has been demonstrated by a number of investigators. Webster and Clow[1] and Webster[2] were able to show that the St. Louis virus could be recovered from the blood of mice almost immediately following subcutaneous inoculation and for twenty-four hours thereafter. After intracerebral inoculation the virus was present in small amounts in the blood immediately following injection and again just prior to death. Hammon and associates[3] have shown that the St. Louis virus is present in the blood of horses from twenty-four to forty-eight hours after subcutaneous inoculation. In connection with a study of the experimental transmission of St. Louis encephalitis virus by mosquitoes, Hammon and Reeves[4] demonstrated virusemia in chickens and ducks forty-eight hours after inoculation by subcutaneous route and from twenty-four to forty-eight hours after being bitten by experimentally infected mosquitoes. In the Syrian hamster, Blattner and Heys[5] have shown that the virus of St. Louis encephalitis is present in the blood from eight to seventy-two hours following intraperitoneal inoculation.

In the case of certain other neurotropic viruses recovery from the blood has been accomplished in human patients as well as in experimental animals. By inoculation of mice, Japanese B virus was isolated from the blood and spinal fluid of a human patient in early stage of infection.[6] Howitt[7] recovered the virus of Western equine encephalomyelitis from stored blood serum taken from an adult whose illness had been diagnosed as encephalomyelitis. Studies of this strain of virus[8, 9] in experimental animals, including the horse, demonstrated that the virus is recoverable during the febrile period from both cardiac and peripheral blood, whole blood and serum. Virus was no longer recovered from the blood after defervescence. Howitt[10] showed that the virus of Western equine was present in the blood from eight to thirty-three hours following nasal

From the Department of Pediatrics, Washington University School of Medicine, and St. Louis Children's Hospital.

instillation in the guinea pig. More recently Gwatkin and Moynihan[11] reported the isolation of Western equine virus from spinal fluid taken ten days after onset of symptoms in a human patient. In Russian encephalitis the virus has been recovered occasionally from the spinal fluid of human patients but is more readily recoverable from the blood.[12, 13]

The virus of lymphocytic choriomeningitis has been recovered with comparative ease from both the spinal fluid and the blood of human patients.[14-16] Experimental inoculation of human volunteers[17] revealed that virusemia begins shortly before onset of fever and persists for twelve to fourteen days.

From the spinal fluid of a patient whose symptoms and signs were suggestive of encephalitis, Armstrong[18] isolated a virus which was identified as a strain of herpes simplex.

On the basis of such observations it seems likely that virusemia does occur in the human patient with encephalitis, but that in many instances the virus is no longer present in the blood stream by the time that symptoms and signs of central nervous system involvement appear. Despite these theoretical considerations, it has seemed worth while to attempt the isolation of virus from the blood stream in this type of patient, and numerous attempts have been made at the St. Louis Children's Hospital to recover virus from blood and spinal fluid of patients with clinical encephalitis.

On July 6, 1945, an 8-year-old boy, resident at Wood River, Ill., twenty miles distant from St. Louis, was admitted on the service of Dr. Alexis F. Hartmann with the following history: During the four days prior to admission, according to the mother, he became extremely drowsy, sleeping all day, rousing intermittently to ask for water. He would fall asleep again almost immediately. Two days before admission, he seemed somewhat improved but had fever and appeared listless. The day before admission he became worse; the temperature rose to 38.9° C., and vomiting was severe. On admission the patient appeared ill and was moderately dehydrated, but the only definite finding was mild pharyngitis. The temperature at the time of admission was 38.2° C. During the course of the examination the boy complained constantly of severe headache. On the way to the admitting ward he seemed disoriented and persisted in sitting in one corner of the elevator. As he was a well-adjusted child, the parents considered this behavior very unusual.

Considering the possibility that this child might have encephalitis, lumbar puncture was advised. The spinal fluid obtained was slightly opalescent and contained 250 lymphocytes. The Pandy was slightly positive. Immediately following lumbar puncture, blood was taken from the antecubital vein, using sterile precautions. Some of the specimen was added to a tube containing the sodium salt of heparin (Lederle), 0.01 ml. to 10 ml. of whole blood; another portion of the blood sample was saved for serum; and a third portion was set aside for antibody study.

After dehydration was corrected, the patient showed marked improvement. Subsequent course in the hospital was unusually mild. At no time were definite meningeal signs noted. Laboratory data revealed the following: Urinalysis, negative; white blood cells, 6,300 with 2 eosinophiles, 8 stabs, 31 segmented cells, 55 lymphocytes, and 4 monocytes. Tuberculin test was negative. The spinal fluid sugar was 81.5 mg. per cent, and simultaneous blood sugar was 95.5 mg. per cent. Lumbar puncture repeated three days after admission showed the presence of 365 cells, 42 per cent of which were lymphocytes. Seven days after admission the lumbar puncture showed 41 cells, all of which were lymphocytes. The patient was discharged in excellent condition on the tenth hospital day. There was no evidence of sequelae.

EXPERIMENTAL FINDINGS

Immediately after lumbar puncture the spinal fluid was inoculated onto the chorioallantoic membrane of four embryonated hen's eggs: two eggs of seven days' incubation; two eggs of twelve days' incubation. There was no evidence of growth on these membranes. After ninety-six hours the chorioallantoic membranes of these four eggs were removed, pooled, and passed to four adult white Swiss mice, 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. These mice remained free of signs during three weeks of close observation. Four 9-day-old white Swiss mice were injected with the original spinal fluid: 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. None of these mice developed signs of illness.

Within five minutes after obtaining the blood sample, heparinized blood was inoculated into six littermates of the 9-day-old mice used for the spinal fluid test, 0.05 ml. of heparinized blood being injected intraperitoneally into each of the six 9-day-old mice. Simultaneously, heparinized blood was injected into four young adult white Swiss mice, 0.1 ml. intraperitoneally, 0.03 ml. intracerebrally. Serum separated from the clotted blood was injected into six young white Swiss mice, 0.03 ml. intracerebrally and 0.1 ml. intraperitoneally. Some of this serum was also injected into eggs: two of seven days' incubation and two of twelve days' incubation. There was no evidence of virus growth on the chorioallantoic membranes. Of the inoculated mice none showed signs of illness except the six 9-day-old mice which had been injected intraperitoneally with heparinized blood.

On the seventh day after inoculation these six mice appeared listless. Within two hours five of them were dead. The one remaining alive was in convulsions. The brain, spleen, and lungs of each of the five were removed, frozen, and stored in a refrigeration unit* maintaining a temperature of –56° C. A small piece of tissue from each organ was cultured in tryptose-phosphate broth. None of these cultures showed bacterial growth. Likewise, the brain, spleen, and lungs were removed from the one mouse remaining alive. Bacterial cultures of tissue in broth remained sterile. The spleen and lungs were frozen and stored. The brain was emulsified in tryptose-phosphate broth and the resulting supernatant fluid inoculated intracerebrally, 0.03 ml., into four young adult mice. Blood agar culture of the inoculum gave no growth. On the ninth day following injection, two of these young adult mice showed signs of illness with convulsive movements. The brain of each was removed, cultured, and passed to four adult mice. Three to five days following this inoculation two of the eight mice were dead; three were in convulsions. The brains from this passage were cultured and passed to other adult Swiss mice. Again within three days definite convulsions were noted. At the present writing the newly isolated virus has been well established in white Swiss mice (ninth passage) and produces convulsions and death in two to three days after inoculation of 0.03 ml. intracerebrally, 10^{-1} suspension. In all passages cultures of blood, brain, spleen, and lung were negative.

*This refrigeration unit was purchased from funds made available by the Children's Research Foundation of St. Louis.

The newly isolated strain of virus is filter-passing: Berkefeld N and V-fine filters. At the second intracerebral mouse passage the virus kills adult white Swiss mice through the 10^{-6} dilution; at the seventh intracerebral passage, the virus kills adult white Swiss mice through the 10^{-8} dilution.

Microscopic sections of mouse brains from the second and the sixth intracerebral passages show an encephalitic process which is apparently indistinguishable from that produced in the mouse by a known strain (Hubbard) of St. Louis encephalitis virus.

The newly isolated virus was inoculated onto the chorioallantoic membrane of the developing hen's egg. Within four to five days definite evidence of virus growth was noted. Passage of egg membrane to mice produced convulsions in three to four days. The newly isolated virus was injected also into a rabbit, 0.06 ml. 10^{-1} suspension intracerebrally. No evidence of illness has been noted. One adult guinea pig was inoculated, 0.1 ml., 10^{-1}, intraperitoneally, and 0.1 ml. 10^{-1} sublingually. A second adult guinea pig received 0.25 ml. of 10^{-1} suspension intraperitoneally. A young guinea pig, approximately 3 weeks of age, was injected with 0.25 ml. of 10^{-1} suspension intraperitoneally. Its littermate received 0.04 ml., 10^{-1}, intracerebrally. Cultures of all inocula were bacterially sterile. There has been no sign of illness in any of these guinea pigs.

Using the newly isolated strain of virus, parallel serum-virus neutralization tests were performed with blood serums obtained from the patient during clinical course and with sera of rabbits immunized against St. Louis encephalitis virus, Hubbard strain, lymphocytic choriomeningitis, and herpes simplex. Controls consisted of mixtures with broth alone and with normal human serum. It will be seen from the results of this test, which are given in Table I, that during

TABLE I. SERUM-VIRUS NEUTRALIZATION TESTS USING NEWLY ISOLATED VIRUS SHOWING INCREASING TITER OF ANTIBODY IN PATIENT'S SERUMS; NEUTRALIZATION OF VIRUS BY ST. LOUIS IMMUNE RABBIT SERUM, LACK OF NEUTRALIZATION BY LYMPHOCYTIC CHORIOMENINGITIS AND HERPES RABBIT SERA*

DILUTIONS OF VIRUS	PATIENT'S SERUM I 4 DAYS AFTER ONSET	PATIENT'S SERUM II 9 DAYS AFTER ONSET	PATIENT'S SERUM IV 28 DAYS AFTER ONSET	IMMUNE RABBIT SERUM LYMPHOCYTIC CHORIOMENINGITIS	IMMUNE RABBIT SERUM ST. LOUIS (HUBBARD)	IMMUNE RABBIT SERUM HERPES (H. F.)	NORMAL HUMAN SERUM	CONTROL BROTH
10^{-2}	3 3 3 3	3 3 3 4	S S S S	3 3 4 4	S S S S	3 3 4 4 4	T 3 3 3	3 3 3 3
10^{-3}	3 3 3 4	S S S S	T S S S	3 3 3 3	S S S S S	3 4 4 4 4	3 3 3 3	3 3 3 3
10^{-4}	3 3 3 3	S S S S	S S S S	3 3 3 4	S S S S S	3 4 4 4 4	3 3 3 4	3 3 4 4
10^{-5}	S S S S	S S S S	S S S S	3 3 3 4	S S S S S	3 4 4 4 4	3 3 4 4	3 3 4 4

*Each figure represents one mouse; figure indicates day of convulsions and death; S = survived; T = died trauma.

the clinical course the patient developed increasing titer of humoral antibody to the newly isolated virus. As is shown also in Table I the virus is not neutralized by lymphocytic choriomeningitis or herpes immune rabbit sera but is neutralized completely by St. Louis encephalitis immune rabbit serum. Another parallel protection test was carried out using the newly isolated strain

TABLE II. SHOWING COMPARABLE INCREASE IN TITER OF ANTIBODY TO THE NEWLY ISOLATED VIRUS ("M" STRAIN) AND TO A KNOWN STRAIN OF ST. LOUIS ENCEPHALITIS VIRUS (HUBBARD)*

DILUTIONS OF VIRUS	PATIENT'S SERUM I 4 DAYS AFTER ONSET	PATIENT'S SERUM IV 28 DAYS AFTER ONSET	NORMAL HUMAN SERUM	IMMUNE RABBIT SERUM ST. LOUIS ENCEPHALITIS	CONTROL BROTH
		"M" Strain of Virus			
10^{-3}	3 3 3 4	S S S S	3 3 3 4	S S S S	3 3 3 3
10^{-4}	3 4 4 4	S S S S	3 3 3 4	S S S S	3 3 3 4
10^{-5}	4 4 4 S	S S S S	4 4 4 4	S S S S	4 4 4 4
		St. Louis Encephalitis (Hubbard Strain)			
10^{-3}	3 3 4 4	S S S S	3 3 3 3	S S S S	3 3 3 4
10^{-4}	4 4 4 5	S S S S	3 3 3 3	S S S S	4 4 4 4
10^{-5}	S S S S	S S S S	3 4 4 4	S S S S	4 4 4 5

*Each figure represents one mouse; figure indicates day of convulsions and death: S = survived.

and a known St. Louis encephalitis strain of virus (Hubbard). The results summarized in Table II show that during his clinical recovery, the patient developed a comparable increase in titer of antibody to the newly isolated strain and to the known St. Louis virus.

Certain aspects of this study are worthy of note. The unusually mild clinical course of this illness, shown to be due to a neurotropic virus, lends support to the contention that many such cases may occur without accurate etiologic diagnosis. Persistence of the virus in the peripheral blood approximately four days after onset of clinical symptoms is considered unusual. It is a matter of conjecture whether any relationship exists between the prolonged virusemia and the paucity of central nervous system manifestations in this patient.

SUMMARY

A filtrable virus has been isolated from the blood of a patient whose clinical manifestations were suggestive of a virus infection with minimal central nervous system involvement. The infectious agent isolated is neutralized by serum of a rabbit immunized to a known strain (Hubbard) of St. Louis encephalitis virus. During the clinical course the patient developed increasing antibody titer to the newly isolated virus and to known St. Louis encephalitis virus (Hubbard).

Two criteria for the diagnosis of a virus disease have been satisfied; namely, isolation of an infectious agent from the patient, and development during the course of clinical illness of type-specific humoral antibodies.

This work represents the first instance of the isolation of the St. Louis encephalitis virus from a human subject during life. It is the fourth instance in which the St. Louis virus has been isolated from natural sources, the first being the initial isolation from human brain tissue taken at autopsy,[19, 20] the second from mosquitoes collected in nature during an epidemic,[21] the third from the bodies of chicken mites collected in nature during a nonepidemic period.[22]

The intraperitoneal injection of young mice with relatively large inocula may prove to be generally applicable for the isolation of virus, especially for the detection of small amounts.

REFERENCES

1. Webster, L. T., and Clow, A. D.: J. Exper. Med. **63**: 433, 1936.
2. Webster, L. T.: J. Exper. Med. **68**: 111, 1938.
3. Hammon, W. McD., Carle, B. H., and Izumi, E. M.: Proc. Soc. Exper. Biol. & Med. **49**: 335, 1942.
4. Hammon, W. McD., and Reeves, W. C.: J. Exper. Med. **78**: 241, 1943.
5. Blattner, R. J., and Heys, F. M.: J. Exper. Med. **79**: 439, 1944.
6. Inada, R.: Gaz. d. Hôp. **111**: 1125, 1938.
7. Howitt, B. F.: Science **89**: 541, 1939.
8. Howitt, B. F.: J. Infect. Dis. **51**: 493, 1932.
9. Howitt, B. F.: Am. J. Pub. Health **29**: 1083, 1939; ibid. California & West. Med. **51**: 317, 1939.
10. Howitt, B. F.: Proc. Soc. Exper. Biol. & Med. **32**: 58, 1934.
11. Gwatkin, R., and Moynihan, I. W.: Canad. J. Pub. Health **34**: 166, 1943.
12. Silber, L. A.: Arch. Biol. Sci., All Union Inst. Exper. Med. **56**: 8, 37, 1939.
13. Chumakov, M. P., and Seitlenok, N. A.: Science **92**: 263, 1940.
14. Rivers, T. M., and Scott, T. F. M.: Science **81**: 439, 1935.
15. Scott, T. F. M., and Rivers, T. M.: J. Exper. Med. **63**: 397, 1936.
16. Rivers, T. M., and Scott, T. F. M.: J. Exper. Med. **63**: 415, 1936.
17. Lepine, P., Mollaret, P., and Kreis, B.: Compt. rend. Acad. d. Sc. **204**: 1846, 1937.
18. Armstrong, C.: Pub. Health Rep. **58**: 16, 1943.
19. Webster, L. T., and Fite, G. L.: Science **78**: 463, 1933.
20. Muckenfuss, R. S., Armstrong, C., and McCordock, H. A.: Pub. Health Rep. **48**: 1341, 1933.
21. Hammon, W. McD., Reeves, W. C., Brookman, B., Izumi, E. M., and Gjullin, C. M.: Science **94**: 328, 1941.
22. Smith, M. G., Blattner, R. J., and Heys, F. M.: Science **100**: 362, 1944; ibid. Proc. Soc. Exper. Biol. & Med. **59**: 136, 1945.

FURTHER OBSERVATIONS OF EPIDEMIC DIARRHEA OF THE NEWBORN

I. Observation of a Biphasic Type of Clinical Course

II. Therapeutic Measures Including Prophylactic and Therapeutic Use of Gamma Globulin*

Robert H. High, M.D., Nina A. Anderson, M.D., and Waldo E. Nelson, M.D.
Philadelphia, Pa.

IN A previous outbreak[1] a group of patients with epidemic diarrhea of the newborn responded remarkably well to a regimen of treatment in which particular attention was directed to the correction of states of acidosis and to the maintenance of fluid balance. Although the infants affected in a subsequent outbreak of the disease were treated according to the same principles, less favorable results were obtained. Some of the infants had a unique course characterized by relapses which frequently terminated in death.

EPIDEMIOLOGY

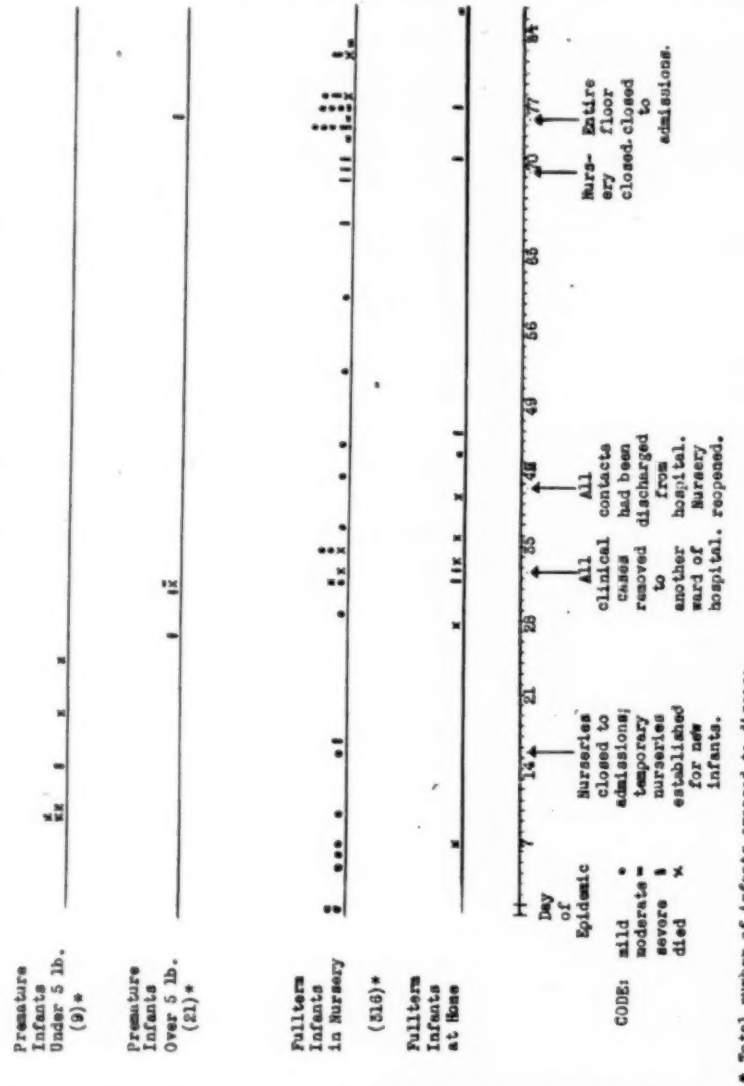
The difficulty of establishing the diagnosis of initial cases of epidemic diarrhea of the newborn was encountered in this outbreak. One infant in each of two nurseries for full-term infants in the Temple University Hospital developed loose stools early in September, 1944. One of them, who had lost considerable weight, was isolated from the other infants, but his subsequent course was uneventful and he was discharged from the hospital on the following day. The other infant, who showed no other evidence of illness, was not isolated until the second day of mild diarrhea, when he had a moderate loss of weight. His subsequent course was also uneventful, the character of his stools improving with modification of the feeding. At the time, therefore, the loose stools of these patients were considered of noninfectious nature, but in retrospect it seems probable that they were the manifestations of the initial mild cases of epidemic diarrhea of the newborn. On successive days other infants in one of these nurseries developed loose stools, and an infant who had been discharged apparently in satisfactory condition one day previously was readmitted to the hospital after the development of diarrhea, vomiting, and loss of weight. The clinical picture of this infant was not typical of epidemic diarrhea of the newborn but resembled that of other infants who had been admitted to the hospital about the same time but who had not had any previous contact with the nursery. Nine days after the first two instances of mild diarrhea, two infants in the premature nursery developed loose stools, on the following day a third infant was similarly affected, and within a short time three other in-

From the Department of Pediatrics, Temple University School of Medicine.

*The name gamma globulin is used for purposes of abbreviation to describe concentrated normal human serum gamma globulin (immune serum globulin) prepared by the methods of plasma fractionation (Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr.: J. Clin. Investigation 23: 417, 1944).

fants in that unit developed the disease. The premature nursery was a separate unit, and there was a separate nursing personnel for it. It was recognized that these infants probably had epidemic diarrhea of the newborn and that in each of the three nurseries others had been inadvertently exposed to the disease.

CHART I. DEVELOPMENT OF CLINICAL CASES IN AN EPIDEMIC OF DIARRHEA OF THE NEWBORN



* Total number of infants exposed to disease.

Clinical cases subsequently developed in both of the nurseries for full-term infants and among the infants who had been dismissed recently from the hospital (Chart I). The nurseries were closed and temporary ones established on

the obstetric floor, all contacts were discharged as quickly as possible and followed at home by their respective physicians, and the infants with the disease were removed to the pediatric ward of the hospital. None of the infants in the pediatric unit, who ranged in ages from 1 to 18 months, developed diarrhea although they were confined in the same general unit with the affected newborn infants. Shortly after the nurseries, which had been thoroughly cleaned after the discharge of all of the exposed infants, were reopened, single mild cases of diarrhea developed at intervals of several days. These infants were isolated promptly even though they did not appear ill; they responded satisfactorily to a modification of the feeding formula and their courses were uneventful. However, these infants undoubtedly had mild epidemic diarrhea of the newborn and transmitted the causative agent to other infants. Complete control of the epidemic was not obtained until the entire department was closed to admissions and was thoroughly cleaned and repainted before it was reopened.

During the relatively long period of time under observation there was a total of 346 infants in the nurseries, of whom 63 developed diarrhea of varying intensity. The morbidity rate was 18.2 per cent. The incidence of the disease, however, was higher among the premature infants than among the full-term ones; six of nine infants in the premature nursery and five of twenty-one infants, ranging in weight from 5 pounds to 5 pounds, 8 ounces, in the other nurseries developed the disease. The average case fatality rate was 23.8 per cent, but it, too, was higher among the premature infants than among those of full-term gestation; 83 per cent (five of six) of the small premature infants, 20 per cent (one of five) of the larger premature ones, and 17.3 per cent (nine of fifty-two of the full-term infants died from the disease. Only 8.7 per cent of the exposed infants weighed less than 5 pounds, 8 ounces, but 36.6 per cent of them developed the disease and in this group of infants 40 per cent of the deaths occurred (Table I).

TABLE I. SUMMARY OF INFANTS AFFECTED WITH EPIDEMIC DIARRHEA OF THE NEWBORN

	TOTAL	FULL-TERM INFANTS	PREMATURE INFANTS		
			UNDER 5 POUNDS	OVER 5 POUNDS	TOTAL
Contacts	346	316	9	21	30
Disease	63	52	6	5	11
Deaths	15	9	5	1	6
Nonfatal cases					
Severe	17	13	1	3	4
Moderate	6	5	0	1	1
Mild	25	25	0	0	0
Morbidity (per cent)	18.2	16.5	66.0	23.8	36.6
Case fatality	23.8	17.3	83.0	20.0	54.5

The ages of the infants at the onset of the disease ranged from three to twenty-two days for the full-term and from five to seventeen days for the premature infants. Since there were multiple contacts for these infants, it is impossible to estimate the incubation period, but its maximum could not exceed the age of the patient at the time of the onset of symptoms. In fifty-one instances the disease was manifest while the infant was still in the nursery while twelve

of them were readmitted to the hospital after developing the disease at home. Three of these, however, had unexplained weight loss in the hospital before discharge, which might have been interpreted as an early symptom of epidemic diarrhea of the newborn. Five of the infants who were readmitted and ten (including five premature infants) remaining in the hospital died.

The only symptom which most of the infants with the mild disease had was loose stools, and the duration of the diarrhea ranged from one to five days; none of these infants had a carbon dioxide combining power lower than 35 volumes per cent, and only four of them lost more than 10 per cent of their birth weight during the hospital course. Among the others the symptoms were more severe; many of them had vomiting and precipitous loss of weight in addition to the diarrheal stools, the duration of which was longer than in the mild cases and ranged from two to seventeen days. All of this latter group had acidosis, which was demonstrated by the determination of a low carbon dioxide combining power. The lowest carbon dioxide determination was 6 volumes per cent, and the greatest weight loss was 31 per cent of birth weight. Eight of the infants had thrush and six, impetigo neonatorum before the onset of the diarrhea or during its course. Two of the infants had both thrush and impetigo. One infant developed osteomyelitis of the femur, another had thrombophlebitis of the saphenous vein, and a third suffered from a terminal sclerema. It was suspected that one of the infants had a congenital heart lesion, which may have contributed to his death. One infant who had septicemia and bowel obstruction with peritonitis developed melena before death.

Cultures were obtained from the stools of the patients, from the nasopharynx of the patients and of attending physicians, nurses, and maids, from the formulas and their ingredients in the formula kitchen, and from blood agar plates exposed to the air for thirty-minute periods in the nurseries, private rooms, wards, formula kitchen, delivery room, labor room, corridors, and nurses' stations. Eighty-six stool cultures were obtained from twenty-nine different patients, eleven nasopharyngeal cultures from patients, and thirty-seven nasopharyngeal cultures from members of the staff. One hundred and eight agar plates were exposed during this period in the places specified. None of these showed growth of a recognizable pathogenic bacterium. Among sixteen blood cultures, coliform bacilli were recovered in four instances in each of which there was also the clinical picture of septicemia. Unfortunately it was not possible to perform virologic studies. There were no herpetic lesions noted in the mouths of any of the infants affected with diarrhea.[2]

Autopsy examinations of ten of the infants did not demonstrate any lesions sufficiently characteristic to differentiate them from those of other forms of enterocolitis. Acute passive congestion of the viscera and terminal pneumonia were found in many of them.

CLINICAL COURSE

Fifty-two patients had a fairly characteristic clinical course, the severity of which ranged from mild diarrhea with no other symptoms to severe diarrhea with marked acidosis, dehydration, prostration, and death in seven instances.

Of eleven patients who had recurrent periods of diarrhea, nine suddenly developed a state of collapse and eight died within a few hours. Six of the infants with this type of clinical course weighed less than 5 pounds, 8 ounces at birth. We have chosen to designate this type of clinical course in epidemic diarrhea of the newborn as "biphasic."

The first phase of this course consisted in the development of diarrhea with moderately severe associated symptoms of dehydration, acidosis, and prostration. After three to five days the character of the stools tended to improve but they did not become entirely normal. However, there were better feeding habits, absence of acidosis, gain of weight, and a better general appearance.

This improvement lasted only a few days and was supplanted by a recurrence in which the acidosis tended to be more severe, the diarrhea more frequent and severe, and the infant obviously more critically ill. In spite of a good oral intake augmented with large amounts of parenteral fluids, the infant would continue to lose weight. After a few days the character of the stools tended to improve and some of them appeared normal. There was sometimes gain of weight, but the general appearance of the infant was not encouraging. After twenty to forty-eight hours of this "pseudo-improvement," the infant suddenly, sometimes within fifteen minutes, went into a state of profound collapse characterized by periods of apnea, weak respirations, evidence of cardiac dilatation, collapse of the peripheral vascular bed, abdominal distention, cyanosis, and death within a few hours. Stimulants and fluids, including adrenal cortical extract and plasma, were ineffective when this state of collapse was reached, except in two instances in each of which improvement occurred when a large quantity of plasma was given rapidly as an intramedullary infusion. The first infant recovered after the injection of almost 300 c.c. of plasma and the second after 200 c.c., only to die in a similar episode one week later.

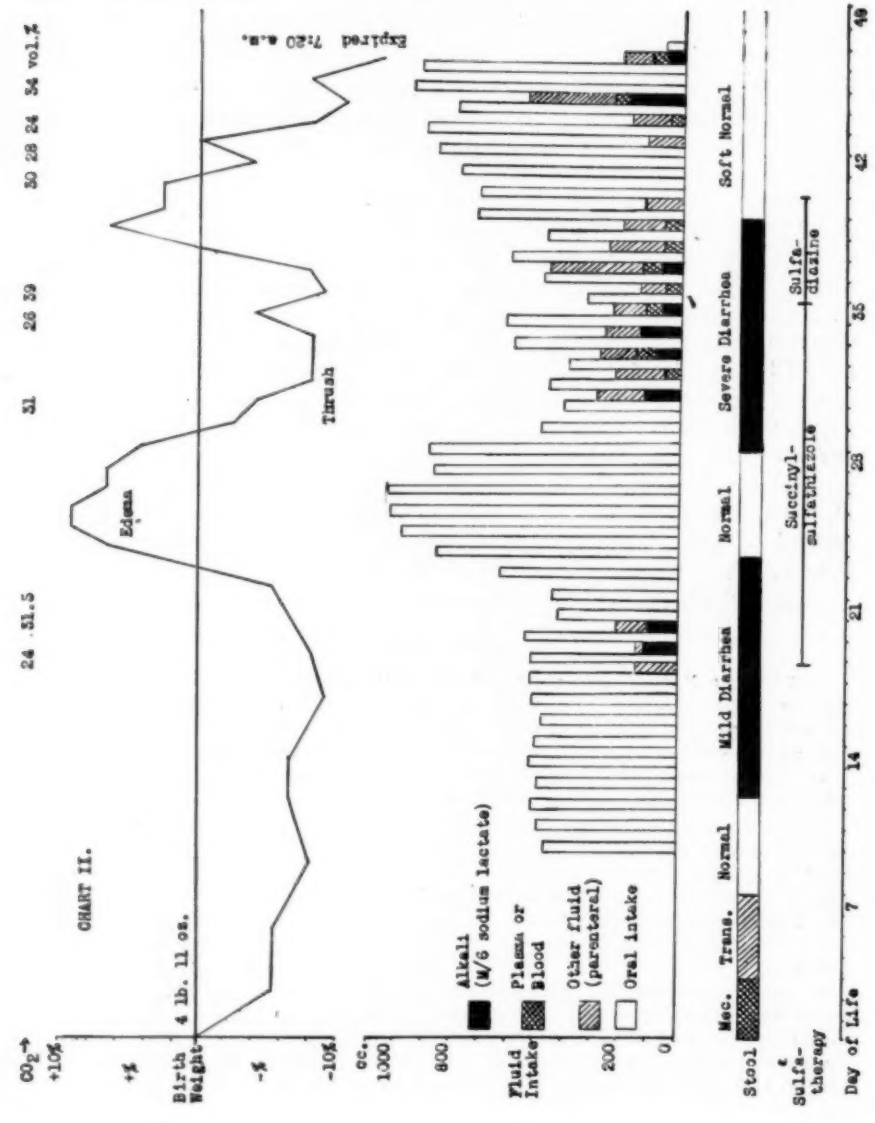
The following case report is illustrative of this type of clinical course:

CASE REPORT

Baby S., a Negro female, weighed 4 pounds 11 ounces at birth; she appeared to be a vigorous premature infant. Her course was uneventful until the twelfth day of life when she occasionally had a loose stool, but never more than one during a twenty-four-hour period. She did not appear ill, and modification of her feeding seemed to control this diarrheal disturbance. To counteract a failure to gain weight satisfactorily she was given a hypodermoclysis of lactate-Ringer's solution.

The first phase of her clinical course of diarrhea began on the nineteenth day of life when she passed another loose stool and had an acidosis (carbon dioxide combining power of 24 volumes per cent) without clinical symptoms, which was corrected by the subcutaneous administration of a calculated amount of one-sixth molar sodium lactate. Later that day her stools became green and liquid; some of them were expelled explosively. She was removed to the Isolation Nursery, but the following day her stools improved in character and became normal during the next faw days. Succinylsulfathiazole (0.25 Gm. daily) was administered orally, and fluid was given parenterally on two occasions. Her general course was uneventful until the twenty-sixth day of life when she began slowly to lose weight from a maximum of 5 pounds. She had had a slight degree of edema, and it was thought that the weight loss might have been accounted for by the disappearance of the edema. Oral moniliasis developed on the twenty-ninth day of life.

The second phase of disease began on the twenty-ninth day of life when she passed a few diarrheal stools. Marked dehydration and acidosis developed rapidly and parenteral fluids, including alkalies, crystalloid solutions, and plasma, were given immediately. There was peripheral vascular collapse, the respirations were rapid and shallow, dehydration was severe, the diarrheal stools were expelled explosively, the abdomen was markedly distended, and there was a moderate degree of cyanosis. After three days the character of the stools was considerably improved, being loose at one time and normal at another. Fluids were administered parenterally, and on the thirty-sixth day of life sulfadiazine was substituted



for succinylsulfathiazole. By the thirty-ninth day of life the stools were normal, the weight had again reached almost 5 pounds, and she entered the period of "pseudo-improvement." Although she took as much as 900 c.c. of formula daily, her general appearance and activity were not encouraging. She began to lose weight in spite of normal stools and of apparently adequate fluid intake. Abdominal distention was severe, and it did not respond to the usual therapeutic measures. On the forty-eighth day of life she suddenly went into a state of shock. Her respirations became short and shallow with occasional long periods of apnea. A loud systolic apical murmur, which had not been heard previously, was audible now. There were peripheral vascular collapse, cyanosis, and listlessness. She did not respond to oxygen, plasma, other fluids, adrenal cortical extract, or stimulants and died from respiratory failure within four hours of the onset of these symptoms (Chart II).

The autopsy revealed an emaciated and dehydrated Negro female infant with a moderately distended but not tense abdomen. The small and large bowels were distended with gas and with liquid fecal matter. Histologically, there was a mild acute enterocolitis, for which there was little gross evidence except for several small indefinite areas of mucosal and serosal hyperemia interspersed between areas of healthy bowel. Other significant findings included subepicardial petechiae and toxic myocardosis; pulmonary atelectasis, interstitial pneumonitis, and early bronchopneumonia; congestion of the liver with mild fatty metamorphosis; congestion of the spleen; toxic nephrosis; inflammatory hyperplasia of the lymph nodes; and interstitial edema of the pancreas and of the thymus.

THERAPY

Epidemic diarrhea of the newborn requires prompt administrative and medical attention for its control. A careful survey should be instituted to seek the cause of the outbreak, and a regimen of treatment outlined for the care of the patients. Affected infants must be isolated, exposed ones segregated, and a new unit, removed from the contaminated obstetric floor, provided for the newborn infants; each group must have a separate nursing staff. Medical supervision and laboratory facilities must be available throughout the day and the night. The treatment of ill infants should include modification of the oral feeding, maintenance of fluid balance, prompt correction of states of acidosis, oral administration of synthetic ascorbic acid and thiamine chloride, and intravenous injections of plasma or of whole blood when indicated.

Attention has already been directed to the significance of weight loss as a symptom which may precede the onset of diarrhea. During this epidemic the practice of weighing the infants in the morning and again in the evening permitted an early recognition of weight loss and prompt administration of parenteral fluid to combat it. Even the infants who take large quantities of fluid orally may need almost equally large amounts of fluid parenterally. On the other hand, marked gain in weight may precede the appearance of demonstrable edema, and its detection warn of the need for plasma or whole blood to prevent fluid retention. The determination of the hemoglobin for detection of hemoconcentration or hemodilution should be employed, since reliance upon the clinical impression alone is frequently not sufficient for an adequate appraisal of the patient's state of hydration.

A large number of the infants received succinylsulfathiazole (0.13 Gm. per pound of body weight per day) either as a prophylactic or a therapeutic measure, but it did not appear to prevent the development or to alter the course of the disease. Many of the infants refused or regurgitated the fluid with which

the drug was mixed, and the stools of the noninfected infants became more mucoid than normal. An absorbable sulfonamide, sulfathiazole or more frequently sulfadiazine, was given to eleven patients, of whom three had a complicating infection for which it was indicated. Its administration, however, did not seem to alter the course of the diarrheal disturbance. Adequate fluid intake and output and alkalinity of the urine must be maintained while sulfonamides are used.

Penicillin was given intramuscularly to six infants in dosages of 50,000 to 100,000 Oxford units daily. In none was the diarrheal disease altered, but the treatment was of value for other coexisting infection. In instances in which septicemia is suspected, it is advisable to use both an absorbable sulfonamide and penicillin since *Escherichia coli*, a penicillin-resistant organism, frequently invades the blood stream.

Perhaps vitamin K should be administered to these patients empirically, in order to prevent any bleeding tendency due to hypoprothrombinemia. It is possible that during the diarrheal disturbance there is an interference with the synthesis of the vitamin by the normal intestinal flora. Vitamin K has been advised as an adjunct to succinylsulfathiazole therapy.[3] Although adrenal cortical extract has been recommended for the treatment of shock, our clinical experience is in accord with that of others who have previously reported the lack of a favorable effect.

USE OF GAMMA GLOBULIN

Gamma globulin* was given to twenty-eight patients. An intramuscular injection of 5 c.c. of gamma globulin was given to each of fourteen infants who had epidemic diarrhea of the newborn or who were suspected of having the disease at that time. An injection of 5 c.c. of gamma globulin was given to fourteen infants who had been exposed to the disease while there were twenty-seven other infants in the nursery who did not receive the injection (Table II).

TABLE II. ADMINISTRATION OF GAMMA GLOBULIN TO INFANTS WITH EPIDEMIC DIARRHEA OF THE NEWBORN

	CONDITION OF THE INFANT AT THE TIME OF THE ADMINISTRATION OF GAMMA GLOBULIN*				CONTROL GROUP†
	NO EVIDENCE OF DIARRHEA	SUSPICIOUS OF DIARRHEA	EPIDEMIC DIARRHEA	TOTAL	
Total No.	14	5	9	28	27
Results:					
No diarrhea at any time	9	0	0	9	22
Suspicious of diarrhea	3	1	0	4	4
Epidemic diarrhea of the newborn	2	4	9	15	1
Died	1	1	0	2	0

*Each infant received 5 c.c. of gamma globulin intramuscularly, except one of those who had the disease, who received 10 c.c.

†Infants exposed to epidemic diarrhea of the newborn who did not receive gamma globulin.

*The products of plasma fractionation employed in this work were prepared by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., from blood collected by the American Red Cross, under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

In this small group none of the infants to whom the product was given as a therapeutic agent improved within a short time after its administration, and more cases of diarrhea developed in the group who received it as a prophylactic agent than in the control group. None of the infants who received gamma globulin developed any local or general reaction following its administration intramuscularly.

DISCUSSION

In this outbreak of epidemic diarrhea of the newborn a number of problems were encountered. Of great importance among these were the ones relating to the detection of the disease and its cause. The mild cases of diarrheal disturbance which developed as the earliest instances in the outbreak were not recognized as epidemic diarrhea of the newborn. Only when more infants were affected, and among them infants with more serious disease, was the insidious onset of the outbreak determined in retrospect. This problem of early diagnosis, could it be solved, would certainly diminish the number of infants inadvertently exposed to the infection and consequently the magnitude of an outbreak. As has been stated previously, whenever the development of diarrheal stools cannot be easily explained on some other noninfectious basis, it would seem advisable to isolate the newborn infant and to consider as a provisional diagnosis epidemic diarrhea of the newborn whenever two or more infants are similarly affected. Such a plan of procedure may abort an impending outbreak of the disease.

To prevent an outbreak of epidemic diarrhea of the newborn is admittedly more important than to detect it. The cause of this outbreak could not be determined from the investigative procedures which were employed. It may be significant that at approximately the same time there was an outbreak of epidemic diarrhea, nausea, and vomiting of unknown cause[4] in Philadelphia among adults. Lyon and Folsom[5] have reported an epidemic of diarrhea of the newborn in a community where influenza was concurrently epidemic. In their series, benefit was obtained from the administration to the infants of blood serum from patients convalescing from the influenzal infection, but no beneficial effect was noted when blood from normal adults was injected. Whether any etiologic relationship among these conditions exists is not known. The best supported evidence up to the present itme for an etiologic agent for epidemic diarrhea of the newborn is that submitted by Light and Hodes[6] in favor of a virus. Unfortunately, we were not equipped to pursue virologic studies during this outbreak. None of the studies which were performed bacteriologically revealed a causative agent. Furthermore, there were no characteristic lesions identified in the pathologic specimens from those infants who were examined postmortem.

Complete control of the outbreak was not obtained until the entire obstetric floor was closed to admissions, thoroughly cleaned, and repainted before it was reopened. Initially the nurseries were closed and temporary ones established elsewhere on the same floor. Other portions of the hospital were already overcrowded with medical and surgical patients, and it was not desired to admit

obstetric patients to those divisions. When a second wave of the disease developed, however, the entire floor was closed to admissions and temporary quarters for the obstetric department established elsewhere in the hospital and staffed by a nursing personnel which was absolutely separate from that charged with the care of the affected and the exposed infants. Since the reopening of the cleaned and repainted department, there have been no instances of this disease among the infants in the nursery.

Epidemic diarrhea of the newborn must always be regarded as a serious disease. Among twenty-eight infants treated for this disease in 1943, there was one death, that of a premature infant. Among sixty-three affected infants in 1944 there were fifteen deaths, of which six were premature infants. In our experience during this more recent outbreak we found that the outcome was less favorable among the small and the premature infants affected with the disease and among the infants who showed a "biphasic" course. It could not be ascertained whether these were instances of relapse or of infection with another microorganism, but the former seems more likely. Significant of poor prognosis are such findings as poor general appearance, persistent diarrhea even if mild, persistent weight loss in spite of a tremendous fluid intake (orally and parenterally), intractable abdominal distention, bleeding tendencies, precipitous weight loss, the appearance of the "biphasic" course, prematurity, complications, and collapse.

In the treatment of this disease the importance of maintenance of hydration and of acid base balance is emphasized again. As previously recommended, chemical evidence regarding acidosis should be sought in all instances in which the infant shows any deviation from the normal pattern since a severe degree of acidosis may be present in the absence of significant clinical signs, which would otherwise not be detected nor treated adequately. The sulfonamides and penicillin did not appear to be effective in the treatment of epidemic diarrhea of the newborn; this is understandable if the etiologic agent is proved to be a virus. Our experience with gamma globulin is limited, and the number of patients treated in this manner is too small to warrant any definite conclusions regarding its value. In the dosage used (5 c.c.) gamma globulin did not retard the development of the disease among infants already exposed to it or alter detectably its clinical course. The role of gamma globulin as an adjunct to the therapy of epidemic diarrhea of the newborn should be investigated further, possibly with larger doses of the product than have been used.

SUMMARY

In an outbreak of epidemic diarrhea of the newborn involving sixty-three infants, there were fifteen deaths. The incidence of the disease and the death rate were higher among the premature infants.

In eleven instances a biphasic clinical course was encountered, in which after clinical and biochemical improvement there suddenly developed ominous symptoms with a state of collapse and death for eight of the infants.

Control of the outbreak was not obtained until the entire department was closed to admissions and thoroughly cleaned before it was reoccupied. An etiologic bacterial agent was not discovered, and virologic studies could not be performed.

Therapeutic measures included maintenance of hydration, correction of acidosis, modification of feeding, and administration of amino acid solution, plasma, and whole blood. Neither sulfonamide nor penicillin therapy seemed to influence the clinical course of epidemic diarrhea of the newborn, and in a limited series the intramuscular administration of gamma globulin had no apparent prophylactic or therapeutic effect.

We wish to thank Drs. J. M. Alesbury, J. O. Arnold, J. B. Bartram, C. T. Beecham, D. Cucinotta, I. Forman, H. Hayford, L. K. Hoberman, M. J. Huffnagle, N. Kendall, T. L. Montgomery, J. P. Quindlen, and C. Reynolds for permission to include data from their patients.

REFERENCES

1. Anderson, N. A., and Nelson, W. E.: J. PEDIAT. 25: 319, 1944.
2. Buddingh, G. J., and Dodd, K.: J. PEDIAT. 25: 105, 1944.
3. Twyman, A. H., and Horton, G. R.: J. A. M. A. 123: 138, 1943.
4. Reimann, H. A., Hodges, J. H., and Price, A. H.: J. A. M. A. 127: 1, 1945.
5. Lyon, G. M., and Folsom, T. G.: Am. J. Dis. Child. 61: 427, 1941.
6. Light, J. S., and Hodes, H. L.: Am. J. Pub. Health 33: 1451, 1943.

A STUDY OF PREMATURE INFANTS OBSERVED IN A PRIVATE HOSPITAL BEFORE AND AFTER THE ESTABLISHMENT OF A PREMATURE NURSERY

ALLAN BLOXSOM, M.D.
HOUSTON, TEXAS

PREMATURE births accounted for 46 per cent of neonatal deaths in the United States in 1941.[1] When the premature neonatal deaths are drastically reduced in a large private maternity hospital through the establishment of a premature nursery, it is interesting to examine the records of those premature infants and to point out the factors that have produced this reduction.

This study was made on a consecutive series of 319 premature infants delivered in the St. Joseph's Maternity Hospital in Houston, Texas, during the period of December, 1942, to December, 1944. On Dec. 1, 1943, a premature nursery was opened in one wing on the top floor of the hospital. The nursery was well isolated from the maternity section and the pediatric department which were located in the same building. The nursery was equipped with ultra-violet lights for protection from air-borne infections. No one with the exception of the nursing personnel was allowed in the main nursery. All examinations by physicians were made in a separate examining room equipped for that purpose. Special nurses trained in the handling of premature infants were employed to care for the infants. At times student nurses have assisted in the care. Warm incubators were kept in the delivery rooms, ready for each premature infant. Oxygen was ordered given routinely until discontinued by the physician or pediatrician in charge.

In the year's period before the opening of the premature nursery there were 160 premature infants delivered, weighing 5 pounds or less. Of this number there were 87 male infants and 73 female infants representing a sex ratio of 120, whereas 106 is the usually quoted term sex ratio. Forty male infants and 48 female infants lived, giving a survival rate of 46 per cent and 66 per cent respectively. As shown in Table I, 54 per cent of the male infants and 34 per cent of the female infants died.

In the year's period after the opening of the premature nursery there were 159 premature infants delivered. Of this number there were 80 male infants and 79 female infants, a sex ratio of 101. Sixty-one male infants and 63 female infants lived, giving a survival rate of 76.2 per cent and 79.7 per cent, respectively. It will be seen in Table II that 23.8 per cent of the male infants and 20.3 per cent of the female infants died.

Since the opening of the nursery there has been a decrease in total premature mortality from 45 per cent to 22 per cent. This represents an annual saving to the community of 36 infants, and inasmuch as each infant is said to be of $9,000 value[2] to the community, this represents a yearly salvage of $324,000.

TABLE I. PREMATURE INFANTS DELIVERED FROM DECEMBER, 1942, TO DECEMBER, 1943

	TOTAL	MALE	FEMALE
Number	160 (100%)	87 (54%)	73 (46%)
Number living	88 (55%)	40 (46%)	48 (66%)
Number dead	72 (45%)	47 (54%)	25 (34%)

TABLE II. PREMATURE INFANTS DELIVERED DECEMBER, 1943, TO DECEMBER, 1944

	TOTAL	MALE	FEMALE
Number	159 (100%)	80 (50.3%)	79 (49.8%)
Number living	124 (78%)	61 (76.2%)	63 (79.7%)
Number dead	35 (22%)	19 (23.8%)	16 (20.3%)

TABLE III. SUMMARY OF DEATHS

YEAR	DELIVERIES	INFANT DEATHS	FULL-TERM DEATHS	PREMATURE	NONVIABLE
1943	5,100	105 (2.6%)	23 (22%)	61 (58%)	21 (20%)
1944	5,036	64 (1.2%)	18 (28%)	38 (59%)	8 (13%)

Table III shows the effect of the decrease in premature deaths on the percentage of total infant deaths in the hospital after the establishment of the nursery.

The percentage of total deaths has dropped from 2.6 per cent in 1943 to 1.2 per cent in 1944. These percentages include all births, viable and nonviable. In this period there was no decrease in the percentage of deaths in term infants, actually a small increase, so that the decrease in total infant deaths was directly due to the salvage of prematurely born infants. There was a significant decrease in the number of nonviable infants born. The number of premature infant deaths was reduced by 36, although the percentage of premature deaths to the total infant death rate remained approximately the same.

Table IV shows the weights at birth in the two-year period 1942 to 1944. It includes the outcome to the infants in each weight group.

TABLE IV. WEIGHTS AT BIRTH

YEAR	1 TO 2 POUNDS		2 TO 3 POUNDS		3 TO 4 POUNDS		4 TO 5 POUNDS	
1943	Total 20		14		36		85	
	Living	Dead	Living	Dead	Living	Dead	Living	Dead
	0	20	2	12	16	20	70	15
1944	Total 5		19		40		95	
	Living	Dead	Living	Dead	Living	Dead	Living	Dead
	0	5	5	14	29	11	90	5

There has been a significant decrease in the number of infants delivered weighing less than 2 pounds. It has been claimed that the war had some bearing on the large number of very small infants and abortions. On the other hand, with the establishment of the premature nursery, and with obstetricians being particularly interested in obtaining larger infants, the decrease in the number of very small infants is in great measure due to their efforts. They have accomplished this by postponing induction of labor in toxemic patients, and those with placenta previa until the fetus is more certainly viable.

There has been a decrease in the deaths of infants in the 3- to 5-pound group. Great credit for this decrease is due, of course, to the nursing personnel. Also the use of sulfonamides and penicillin, and the introduction of the routine use of oxygen, as later shown, are believed to have had their effect on this reduction.

Table V shows the time of deaths of the premature infants in this series.

TABLE V. TIME OF DEATHS OF PREMATURE INFANTS

YEAR	UNDER 24 HOURS	UNDER 48 HOURS	UNDER 96 HOURS	OVER 96 HOURS
1943	38 (53%)	4 (6%)	5 (7%)	25 (34%)
1944	20 (58%)	5 (14%)	5 (14%)	5 (14%)

The increased use of penicillin and of sulfadiazine had some beneficial influence on the mortality rate in 1944. In 1943 seven infants had sulfadiazine or penicillin and 62 deaths occured. Only two of the infants who died had had a sulfonamide. In 1944, 31 infants had a sulfonamide derivative or penicillin and only 35 deaths occurred; of the 35 deaths only 5 occurred after 96 hours of life. Approximately four times the number of infants had penicillin or a sulfonamide in 1944 as in 1943, and the incidence of mortality has been cut more than 50 per cent.

Table VI shows the type of feedings and mortality.

TABLE VI. TYPES OF FEEDINGS

YEAR	BREAST MILK		COW'S MILK FORMULA	
	LIVING	DEAD	LIVING	DEAD
1943	51 (91%)	5 (9%)	33 (60%)	23 (40%)
1944	69 (91%)	7 (9%)	47 (87%)	7 (13%)

In both years the premature infants given breast milk showed a consistently higher rate of survival as compared with those given a cow's milk formula. Breast milk was particularly effective as compared with cow's milk formula before the premature nursery was opened. The establishment of a breast milk bank in this hospital, so that breast milk was available at all times for premature infants, has been of considerable value.

TABLE VII. INFANTS RECEIVING OXYGEN

YEAR	NUMBER RECEIVING OXYGEN	DEATHS
1943	113 (71%)	72 (45%)
1944	156 (98%)	35 (22%)

The routine use of oxygen, or an oxygen and helium mixture, until discontinued by a physician, was employed in the year, 1944, in which there was a sharp reduction in deaths of premature infants. The start of oxygen therapy was not waited until the infant developed cyanosis.

COMMENT

Rascoff[3] reported that with the establishment of a premature nursery in an obstetrical hospital the premature infant mortality rate was reduced 55

per cent. The establishment of a premature nursery in a large maternity hospital in Houston, Texas, resulted in a decrease of 51 per cent in the premature infant mortality rate. The training and interest of the nursing personnel have been great factors in this reduction. This has been well recognized in the past. Certain other factors can be of value in the reduction of the mortality in this type of infant. The interest of the obstetrician in obtaining a larger and more certainly viable infant is of great importance. Premature infants given breast milk, both before and after the start of the nursery, in this series showed the greater chance of survival. The group of infants receiving treatment with one of the sulfonamides or penicillin had the lower mortality. The year the premature infants received oxygen routinely from birth until discontinued by physician showed the lower mortality rate.

SUMMARY

The premature infant mortality rate was reduced 51 per cent in a large maternity hospital through the establishment of a premature nursery.

The factors operable in this reduction have been indicated to be:

A. The training and interest of the nursing personnel

B. The interest of obstetricians in obtaining larger and more certainly viable infants

C. The use of breast milk as the initial feedings for the premature infants

D. The routine use of oxygen immediately after delivery without waiting for the development of cyanosis

E. The use of a sulfonamide or preferably penicillin routinely in all instances of atalectasis or in infants of mothers having immediate prenatal infections

F. The institution of aseptic nursery technique together with ultraviolet irradiation to prevent air-borne infections.

The economic value of a premature nursery to a hospital and community, to mention nothing of the saving of mental anguish to numbers of individuals, is in direct proportion to the number of premature infants delivered in that institution.

I wish to thank Dr. A. L. Dippel for his many valuable suggestions in the preparation of this report.

REFERENCES

1. U. S. Department of Labor, Children's Bureau, Chart No. 1 M 41-5.
2. Laux, J. D.: J. A. M. A. 124: 1054, 1944.
3. Rascoff, Henry: Arch. Pediat. 57: 349, 1940.

SALMONELLA CHOLERAESUIS (VARIETY KUNZENDORF) BACTERIEMIA COMPLICATING STREPTOCOCCAL SORE THROAT

ERWIN NETER, M.D., AND RUTH F. KRAUSS, M.D.
BUFFALO, N. Y.

THE investigations into the antigenic structure of the paratyphoid bacilli have greatly stimulated clinical interest in human salmonellosis. It is now firmly established that *Salmonella* infections in man are much more common than it was believed even a decade ago, that many of the more than 100 different species belonging to the genus may cause disease, and that various species are responsible for any of the three clinical syndromes, namely, (1) *Salmonella* fever, (2) *Salmonella* septicemia or bacteriemia and (3) *Salmonella* gastroenteritis or enterocolitis.

Attention has been called in the past to the fact that *Salmonella* bacteriemia may develop following other maladies. It is likely that in some instances the two diseases were independent of each other. In other cases, however, a pathological process or operative procedure may have caused a decrease in the resistance of the individual to the *Salmonella* organism and thus contributed to its invasion of tissues and blood. Moreover, the changes brought about by the paratyphoid bacillus may be masked by the other infectious process and thus escape proper recognition. The relationship between salmonellosis and preceding or concomitant diseases is worthy of further study. For this reason, a case of *Salmonella choleraesuis* (variety Kunzendorf) bacteriemia complicating or concurrent with streptococcal sore throat is presented here.

REPORT OF A CASE

R. S., a 10-year-old white male, was admitted on June 30, 1945, to the Pediatric Service of Drs. Marvin Israel and Norman C. Bender of the Children's Hospital. The past history revealed that the patient had had measles and frequent attacks of tonsillitis. Two days prior to admission the patient complained of headache and malaise. He had fever and also emesis on one occasion. On admission the temperature was 105.6° F., the pulse rate 110 per minute, and the respiratory rate 40 per minute. The pertinent findings on physical examination were as follows: The tonsils showed numerous ulcerative lesions and were covered with purulent exudate. The anterior cervical lymph nodes were enlarged. No further abnormalities were noted. The urine was normal. Kahn, tuberculin, and Schick tests were negative. The spinal fluid, obtained on the second hospital day, was found to be normal. On the basis of these findings the patient was treated for acute sore throat. Sulfadiazine (1 grain per pound of body weight per twenty-four hours) was given by mouth. The throat was irrigated with warm saline solution. On the second hospital day the temperature of the patient was 102° F.; the patient became comatous and, for several hours, presented a shocklike picture. For that reason, glucose (5 per cent) in physiologic saline solution was given intravenously and sodium sulfadiazine (1 grain per pound of body weight per twenty-four hours) was administered subcutaneously. His condition improved. Sulfadiazine therapy by mouth was resumed on the third day and continued until the eleventh hospital day. The patient made a complete recovery.

From the Departments of Bacteriology and Pediatrics of the Children's Hospital.

The throat culture on admission revealed the presence of numerous hemolytic streptococci. A blood culture taken at that time proved to be positive for *S. choleraesuis* (variety Kunzendorf); there were 25 colonies per cubic centimeter of blood. On the basis of these laboratory findings, a diagnosis of streptococcal sore throat concomitant with or complicated by *S. choleraesuis* bacteriemia was made.

The accompanying chart (Fig. 1) presents the pertinent findings throughout the course of the illness.

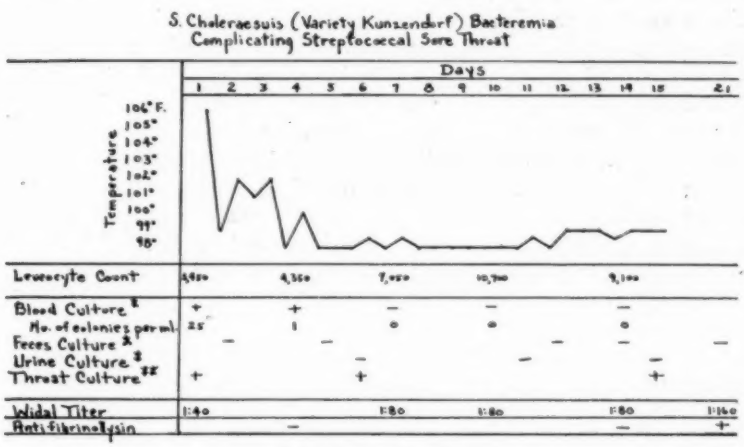


Fig. 1.

One week after discharge from the hospital the patient was seen at the Out-Patient Department. The patient complained of sore throat. The throat was injected. No other pathologic findings were obtained on physical examination. The throat culture revealed the presence of scattered hemolytic streptococci. Antifibrinolysin was present in the blood. The patient's serum agglutinated *S. choleraesuis* (variety Kunzendorf) in a dilution of 1:160. Culture of the feces was negative for *Salmonella*.

Two weeks later, Aug. 5, 1945, the patient developed diarrhea which lasted for one day. It is said that blood and mucus were not present in the feces. He was seen on the following day. At that time the throat was still injected; no other abnormalities were noted on physical examination. The throat culture showed scattered hemolytic streptococci. Antifibrinolysin was still present in the patient's serum. A culture of the feces was negative for *Salmonella*. The titer of agglutinins for the homologous microorganism was 1:160.

DISCUSSION

Recent reports in the literature indicate that *Salmonella* bacteriemia or septicemia may develop as a complication of other maladies. In 1937, in a review of the literature and his own observations on *Salmonella suipestifer* infection of man, Harvey[1] pointed out that this disease may be associated with other illnesses such as tuberculosis, pharyngitis, cystitis, rheumatic heart disease, myomas of the uterus, hypernephroma, rickets, and congenital heart disease. Since then, several reports have been published indicating that certain pathologic processes may favor the invasion of the blood by *Salmonella*

organisms. Four patients observed by Jager and Lamb[2] were debilitated prior to the onset of the *Salmonella* infection, either by previous illness or chronic alcoholism. An excellent illustration for this mode of pathogenesis of *Salmonella* infection is the case observed by Ravitch and Washington.[3] This patient developed *Salmonella* bacteriemia and meningitis secondary to meningococcal meningitis. In 1942, Neter reported a case of *S. choleràesuis* bacteriemia complicating scarlet fever. It was assumed that the hemolytic streptococcal infection predisposed to the secondary infection by a strain of *S. choleraesuis* of low virulence, but empowered with invasiveness. Analagous conditions probably existed in the case presented in this communication. The diagnosis of streptococcal sore throat in the present case is based on the clinical findings, the presence of numerous hemolytic streptococci in the throat, and the development of antifibrinolysin during the course of the illness. The diagnosis of *Salmonella* bacteriemia was made solely on the basis of routine blood culture examinations. This organism, which was identified by Dr. Erich Seligmann of the New York Salmonella Center, was recovered on two occasions. On the day of admission, 25 organisms per cubic centimeter were present in the blood. Three days later the number of bacteria had decreased to one per cubic centimeter of blood. Compatible with the diagnosis of *Salmonella* bacteriemia is the observation that leucopenia persisted in spite of the concurrent streptococcal infection. It is interesting to note in this connection that, according to Harvey,[1] in adults who suffered from *Salmonella* infection and an associated disease the white cell count varied according to the nature of the accompanying illness. Leucocytosis existed in the two patients suffering from *Salmonella* bacteriemia concurrent with scarlet fever and meningococcal meningitis, respectively (Neter[4, 5]).

It is the experience of all observers that the primary focus of infection in sporadic cases of *Salmonella* bacteriemia usually cannot be discovered. Throat, feces, and urine cultures on the patient reported herein failed to reveal the presence of *Salmonella* organisms. No evidence was obtained that diarrheal disease existed among the relatives or possible contacts prior to the illness of this patient.

The question arises as to whether or not the invasion of the blood stream by *S. choleraesuis* took place from the throat which was infected by hemolytic streptococcus. As mentioned before, a search for paratyphoid bacilli in the material obtained from the infected tonsils failed entirely. Recent investigations by Varela and Olarte[6] as well as Hormaechea and Peluffo[7] prove beyond doubt that *Salmonella* organisms may be present in the oral cavity, in carriers and patients with *Salmonella* infection. In the latter instance, the oral cavity may be the primary focus of infection or the organ of elimination of the microorganism.

A study of the antibody response of the present case revealed the development of agglutinins in only moderately high titer. The serum of the patient obtained on the day of admission to the hospital caused agglutination of the homologous organism in a dilution of 1:40. At that time *S. choleraesuis* was present in the circulating blood. Three weeks later the titer was 1:160.

This titer may be considered significant, particularly in view of the observations of Gouldner, Kingsland, and Janeway[8] to the effect that the sera of thirty-four normal subjects failed to agglutinate *S. choleraesuis*. Rubenstein, Feemster, and Smith[9] found an increase in titer of agglutinins in 42 per cent of fifty patients suffering from group C *Salmonella* infections. That agglutinins in high titer may develop in some patients with *Salmonella* infections is evidenced by the observations of Seligmann, Saphra, and Wassermann,[10] who encountered titers up to 1:6,400. However, not all patients with *Salmonella* infections, or even *Salmonella* bacteriemia, develop demonstrable antibodies against the homologous microorganism (Jager and Lamb,[2] and others).

SUMMARY

A case of *S. choleraesuis* (variety Kunzendorf) bacteriemia complicating or concomitant with streptococcal sore throat is described. The relationship of the two diseases is discussed.

The authors wish to express their appreciation to Dr. Erich Seligmann, New York Salmonella Center, for identification of the *Salmonella* organism.

REFERENCES

1. Harvey, A. M.: Arch. Int. Med. 59: 118, 1937.
2. Jager, B. V., and Lamb, M. E.: New England J. Med. 228: 299, 1943.
3. Ravitch, M. M., and Washington, J. A.: J. A. M. A. 109: 1122, 1937.
4. Neter, E.: Am. J. Dis. Child. 64: 255, 1942.
5. Neter, E.: J. PEDIAT. 23: 562, 1943.
6. Varela, G., and Olarte, J.: Rev. d. Inst. salub. y enferm. trop. 3: 289, 1942.
7. Hormaeche, E., and Peluffo, C. A.: Rev. argent.-norteam. cien. méd. 1: 115, 1943.
8. Goulder, N. E., Kingsland, M. F., and Janeway, C. A.: New England J. Med. 226: 127, 1942.
9. Rubenstein, A. D., Feemster, R. F., and Smith, H. M.: Am. J. Pub. Health 34: 841, 1944.
10. Seligmann, E., Saphra, I., and Wassermann, M.: Am. J. Hyg. 38: 226, 1943.

PRELIMINARY OBSERVATIONS ON SOME CHILDREN WITH RHEUMATIC HEART DISEASE TRANSPORTED TO A SUBTROPICAL CLIMATE

JOHN J. ROBINSON, M.D., BETHESDA, MD., AND JAMES H. CURRENS, M.D., BOSTON, MASS.

COBURN[1] very effectively called attention to the helpful climatic effects in children with recurrent rheumatic fever; this was soon followed by Roche and Jones[2] bringing some half dozen rheumatic cardiac children from Boston to Miami Beach during the winter months for three years. The problem of the transportation of rheumatic fever patients to a subtropical climate[3] is not a simple nor sure one. Nichol[4] has shown in a study of the geographic distribution of rheumatic fever in the United States that the rate in southern Florida is about one-tenth that of the average northern rate. On the other hand, rheumatic recurrences do occur in an ideal tropical climate[5] and rheumatic heart disease exists among native Miami children.

This preliminary report is based on eighty-eight children, from 6 to 16 years old, who were brought to Miami from 1938 to 1945 and spent a total of 114 patient-years in the National Children's Cardiac Home amid sanitarium surroundings. Very likely, at least 1,000 patient-years will be necessary to form statistical conclusions within a 10 per cent range of accuracy. Because of both the current extremely divergent views on climatic effects and also the considerably expanding importance of institutional care for the rheumatic child, our early findings appear to warrant reporting.

Two main factors affected our group of patients: first and probably more important, that of specialized sanitarium care; second, a rather ideal, even, subtropical climatic environment. Our care is comparable to that of most of the larger northern institutions[6] devoted exclusively to children with rheumatic fever and rheumatic heart disease. Briefly, therapy consists largely of careful medical evaluation, adequate rest, abundant nourishing food, special educational and recreational programs, and salicylates rather conservatively administered where indicated. No sulfonamide prophylaxis is employed. Only northern children with definite, uncomplicated rheumatic heart disease are admitted; and, being a charity institution, those of the lower income brackets. While active cases of rheumatic infection are accepted, a child must be reasonably well to make the trip to Miami. Our data are summarized in Tables I and II.

Only one recurrence was characterized by more than a very slight amount of arthralgia, and that lasted less than one week; one recurrence followed tonsillectomy a month previously; six of the seven cases of recurrence, judged by Jones's[8] criteria, would have escaped ordinary detection and were found through routine erythrocyte sedimentation rate tests, observation of graphic temperature and pulse charts, along with our perhaps acutely conscious attention to

TABLE I

1. Number of patients with rheumatic heart disease who have been in the National Children's Cardiac Home at least one month, 1938-1945: 88
2. Average year of birth: 1931
3. Average stay: 15.6 months; total patient-years: 114
4. Average cardiothoracic index[7]
   a. On admission: 48.0
   b. On discharge: 46.6
5. Active rheumatic fever on admission: 13 cases, or 14.8 per cent.
6. Active rheumatic fever on discharge: 2 cases, or 2.3 per cent
7. Active rheumatic fever recurrences: 7 cases, or 7.9 per cent
8. Improvement on discharge: 86 cases, or 98 per cent

TABLE II. TYPES OF HEART DISEASE

TYPE	NO.	PER CENT
1. All cases of MI	78	89.0
a. MI alone	33	37.5
b. MI plus MS	13	14.8
c. MI plus MS plus AI	19	21.6
d. MI plus AI	10	11.4
2. All cases of MS	35	39.8
a. MS alone	1	1.1
3. All cases of AI	32	36.4
a. AI alone	2	2.3
4. No cases of MS plus AI alone, or of AS		

MI, mitral insufficiency; MS, mitral stenosis; AI, aortic insufficiency; AS, aortic stenosis.

minor symptoms. None followed any detectable respiratory infection, and no discernible precipitating factor was apparent in these cases.

Several instances of very striking improvement occurred, such as functional improvement from a serious aortic insufficiency, considerable decrease in heart size, and general excellent physical improvement. Such instances have also been noted by Dr. Taussig at Baltimore; they deserve only a brief passing word at present.

We have constantly observed about as many cases of colds, bronchitis, virus pneumonia, measles, mumps, and chicken pox as previously seen in clinical experience in the North; severe streptococcus infections were conspicuously rare. Neither scarlet fever nor severe acute tonsillitis was encountered; they appear to be unusual in South Florida. Low-grade streptococcus infections, such as chronic tonsillitis and impetigo, were about as frequent. Throat cultures made nearly once a month the past two years have shown a 10 per cent to 20 per cent incidence of beta hemolytic streptococci the year around. From all this, we surmise streptococcus infection to exist at Miami in a milder form than in the North; and that respiratory infections from other causes are not as capable of inciting an attack of rheumatic fever.

Our experience leads us to believe that a subtropical or tropical climate is more salubrious for the rheumatic fever patient but far from curative. Transporting such patients to a climate such as South Florida should be considered as a prophylactic measure, since fewer and milder recurrences of the disease mean less cardiac damage. Under these circumstances, we are in a position to encourage such an undertaking for the rheumatic patient, but we wish to deplore

attempting to send seriously ill patients over long distances in an attempt to gain small advantage over the active disease. Such effort is, in our experience, misspent and is usually more harmful than good.

With the great economic and social obstacles involved in long transportation, plus home separation, treatment in sanitariums in the South will by no means be the completely satisfactory answer to the rheumatic fever problem. Such will come only from more complete knowledge regarding the pathogenesis of the disease and more effective therapeutic measures during the active phase of the disease. However, as a prophylactic measure, transfer to a subtropical climate may in certain cases be lifesaving and can be highly recommended. The additional change in many instances from poor home environment to good sanitarium care is remarkably beneficial.

SUMMARY

A preliminary report is presented giving our experience with the care of patients with rheumatic heart disease in a subtropical climate amid sanitarium surroundings. The nature of benefit derived from such a climate is primarily prophylactic against repeated and serious recurrences of the disease. Transfer of seriously ill patients with active rheumatic fever is not recommended. The beneficial effect of sanitarium care is stressed.

REFERENCES

1. Coburn, A. F.: Factor of Infection in the Rheumatic State, ed. 2, Baltimore, 1933, Williams and Wilkins Company.
2. Roche, C. F., and Jones, T. D.: J. Fla. M. A. 20: 342, 1934.
3. Jones, T. D., White, P. D., Roche, C. F., Purdue, J. J., and Ryan, H. A.: J. A. M. A. 109: 1308, 1937.
4. Nichol, E. S.: J. Lab. & Clin. Med. 21: 588, 1936.
5. Hyman, A. G.: Ann. Int. Med. 22: 639, 1945.
6. Taran, L. M.: J. PEDIAT. 23: 69, 1943.
7. Taussig, H. B., and Goldenberg, M.: Am. Heart J. 21: 440, 1941.
8. Jones, T. D.: J. A. M. A. 126: 481, 1944.

RATBITE FEVER

C. G. WATKINS, M.D.
DURHAM, N. C.

RATBITE fever, apparently known in India for 2,300 years, was first reported in the United States by Wilcox[1] in 1840. Since Schottmüller,[2] in 1914, described a streptothrix as the cause of a case of ratbite fever and Futaki and associates,[3] in 1916, demonstrated a spirochete, there has been a great deal of controversy as to which organism was the true etiological agent. However, in recent years both the *Streptothrix muris ratti* (later named the *Streptobacillus moniliformis* by Levaditi and associates[4] in 1925) and the *Spirochaeta morsus muris* (later renamed the *Spirillum minus* Carter, 1887, by Robertson[5] in 1924) have been recovered from patients suffering from clinical ratbite fever, and this disease is currently considered to have a dual etiology.* Blake[6] (1916) reported the first case in the United States caused by the streptobacillus, and Shattuck and Theiler[7] (1924) reported the first case in the United States caused by the spirillum. Bayne-Jones[8] presented a brief summary of the first eighty-one cases in the United States from 1840 to 1930. Brown and Nunemaker[9] reported four additional cases prior to 1931 and forty cases from 1931 to 1940; they also compiled all of the cases occurring in the United States up to 1940 in which the causative organisms were actually demonstrated.

The *Streptobacillus moniliformis* (the name indicates chains of bacilli interspersed with beaded swelling)[9] is a very pleomorphic, gram-negative, nonacid-fast rod which usually appears straight but occasionally fusiform and varies from 2 to 15 microns in length.[10] Branched forms have been described,[6, 11, 12] but several recent investigators have not been able to demonstrate true branching.[9, 13] Brown and Nunemaker[9] have determined that the basic structure is some sort of "small body," neither a coccus nor a bacillus, which appears linked with other bodies in a chain to produce a segmented filament. These granular filaments have a marked tendency to fragment and therefore do not have uniform length. Large round bodies along the course of the segmented filaments probably contain the viable elements of the culture.

This organism has been identified as the etiological agent not only in ratbite fever, but also in Haverhill fever, which is an epidemic disease, usually milk-borne, but sometimes of unknown source, characterized by petechial rash, arthritis, and septicemia.[9] Bronchopneumonia caused by this organism has been reported in mice and rats,[14] and therefore the respiratory tracts of these animals probably serve as the sources of this organism at the time of ratbite.

The *Spirillum minus* is an organism which consists of a spiral, short, thick body, 2 to 5 microns in length, with terminal flagella which increase the length to 6 to 10 microns. It is thicker than the *Treponema pallidum* and usually

From the pediatric service of the St. Louis City Hospital.

Presented in part at the meeting of the American Academy of Pediatrics, Nov. 9, 1944, in St. Louis, Mo.

*Henceforth, reference will be made only to the *Streptobacillus moniliformis* and the *Spirillum minus*.

presents one curve per micron, the curves being regular and sharp.[15-18] It moves rapidly across the field of vision by spasmodic spiral movements of the body and whipping, winding, darting movements of the flagella.[15] Excellent photomicrographs of the spirilla have been presented in several reports.[18-20]

Most cases of this type of infection follow ratbite; however, several cases have been due to other immediate or unknown sources. The best evidence indicates that the source of spirilla at the time of ratbite is the eye discharge produced by the interstitial keratitis and conjunctivitis of the infected rat; this discharge, from which spirilla have been demonstrated, drains into the mouth of the rat.[16, 21]

It seems timely to introduce several terms for general use. The term "spirillary fever" could be used to include all cases of infection due to the *Spirillum minus*. "Spirillary ratbite fever" could be used as the specific term to indicate ratbite fever due to the *Spirillum minus*. "Streptobacillary fever" could be used as an inclusive term; that is, including those cases associated with ratbite (animal bite) and cases of Haverhill fever. "Streptobacillary ratbite fever" could be used as the specific term to indicate ratbite fever due to the *Streptobacillus moniliformis*.

TABLE I. CHARACTERISTICS OF BOTH TYPES OF RATBITE FEVER

	STREPTOBACILLARY	SPIRILLARY
1. Portal of entry	Animal bite*	Animal bite
2. Incubation period	1 to 22 days (usually less than 10 days)	4 to 28 days (usually more than 10 days)
3. Primary wound	Occasional swelling; usually prompt healing	Prompt healing followed by an indurated ulcer
4. Lymphadenitis	Occasional regional	Frequent regional
5. Fever	Septic, occasional relapsing	Relapsing
6. Rash	Morbilliform; petechial	Roseolar-urticarial (bluish red plaques)
7. Arthritis	Common (70%)	Rare
8. White blood count	10,000-30,000/cu.mm.	5,000-30,000/cu.mm.
9. Serologic tests for syphilis	False positive, 16%	False positive, 51%
10. Complications	Respiratory symptoms; abscesses; endocarditis	Nephritis; endocarditis; herxheimer reaction
11. Mortality	10%, 4 deaths in 39 cases	7%, 3 deaths in 41 cases
12. Therapy	Sodium aurothiomalate; penicillin	Arsenical compounds; penicillin

*Milk-borne infection in Haverhill fever.

A comparison of the two forms of ratbite fever is presented in Table I which is a compilation of the characteristics of the two diseases from several reviews in the past[8, 9, 22-24] and from a personal review of all reported cases since 1940. The most prominent difference is the frequency of arthritis in streptobacillary infection as contrasted to the very low incidence in spirillary infection. A short incubation period, a septic type of fever, and the presence of petechiae and abscesses point to the probable diagnosis of streptobacillary ratbite fever; whereas, a long incubation period, a relapsing type of fever, and induration and/or ulceration of the primary wound should lead one to suspect a spirillary infection.

Approximately fifty cases of ratbite are seen in the Receiving Room of St. Louis City Hospital each year. During the past eight years, sixteen cases of clinical ratbite fever were seen in the hospital and in six of these cases, the causative organism was demonstrated. Three of the bacteriologically proved cases were seen in 1944 and were of such interest as to warrant being considered in detail.

CASE 14.—E. N. (26849), a 5-month-old white female, admitted to the pediatric service on April 17, 1944, had been bitten by a rat twelve days previously, when her mother had also been bitten by a rat. Her sister had had a rat bite in 1943 but had not become ill.

The patient had been bitten in several places around the mouth (chiefly on the left side of the upper lip) and on the left hand. These were "sore" for a few days, then had healed. The child was apparently well for a week, until the day before admission when her upper lip and left thumb were noted to be swollen. She appeared feverish and ate very little. On the day of entry she became very drowsy and that afternoon had a fever of 102° F.

Examination on admission revealed a well-developed and well-nourished female infant who had a temperature of 100° F. and a papular erythematous rash over the left arm and chest. These papular lesions were solitary, blanched on pressure, varied from 5 mm. to 1 cm. in diameter, totaled twenty to twenty-five in all, and were chiefly on the left arm. There was no regional or general lymphadenopathy. Over the left eye there was a swollen, indurated area where definite bite scars could be seen. The left side of the upper lip was swollen and indurated, and a gray plaque was present in the center of a chancrelike ulcer on the inner surface of the lip. The distal phalanx of the left thumb was swollen on the volar surface; this area was red and fluctuant. A small denuded area was present on the palm. There was no arthritis.

Blood culture, taken on admission, revealed a *Staphylococcus aureus*, which fermented mannite. The blood Kahn and Wassermann tests were negative. The following day the blood count revealed: red cells, 4,060,000 per cubic millimeter; white cells 14,600 per cubic millimeter; and hemoglobin, 9.0 Gm. per cent. Differential white count showed 3 juvenile; 5 stab, and 38 segmented forms; 52 lymphocytes; and 2 monocytes. Urinalysis was negative.

On the day after entry, typical *Spirillum minus* organisms were demonstrated by dark-field examination of the lymph from the chancrelike lesion of the upper lip.* Lymph from this lesion, lymph from the lesion on the left thumb, and blood from the patient were inoculated intraperitoneally into three separate stock mice. Daily dark-field examinations of the peripheral blood of the inoculated mice were negative from the sixth day after inoculation until the ninth day, when *Spirillum minus* organisms were seen in the peripheral blood of the mouse inoculated with the lymph from the lesion on the lip. On the following day, these organisms were also demonstrated in the mouse inoculated with the patient's blood. The mouse inoculated with the lymph from the left thumb was reinoculated seven days later and died in approximately two days. On the day following the second inoculation, dark-field examination of the peripheral blood of this mouse revealed chains of bacilli of varying size; several of these organisms appeared to be branched.

As the infant did not appear to be critically ill, it was decided to observe the expected relapsing temperature course of the disease, and therefore arsenical therapy was postponed. An irregular relapsing temperature course of low grade character was noted during the next week. On the eighth hospital day, the lesions on the lip and thumb were noted to have become worse. The temperature rose to 102.5° F. that evening. Neoarsphenamine (0.0325 Gm., 5 mg. per kilogram) was given intravenously. The temperature continued up to 103.8° F. during the early morning of the following day, when it was noted that the lesions on the lip, left thumb, and above the left eye seemed to be more swollen and

*Demonstrated by Mr. W. H. Gabby, Snodgras Laboratory, St. Louis City Hospital, St. Louis, Mo.

inflamed. Direct dark-field examination of the lymph from the upper lip was negative approximately eighteen hours after the injection of neoarsphenamine. That evening the patient appeared much improved; the temperature had fallen to 100.5° F. The bluish red color and swelling of the lesions had decreased markedly. The patient vomited occasionally during the first nine days of hospitalization (having lost a total of 600 Gm. in weight) and vomited frequently on the tenth day. Blood Kahn and Wassermann tests had been negative on three different occasions during the hospital stay and both were reported as doubtful on the tenth day. Blood count on this day revealed the following: red cells, 4,800,000 per cubic millimeters; white cells, 32,000 per cubic millimeter; and hemoglobin, 10 Gm. per cent. That evening the patient appeared pale and comatose and began to have short, irregular respirations. Physical examination and a roentgenogram of the chest did not reveal any further positive findings. The patient expired at 8:30 P.M., April 27, 1944.

Autopsy, performed by the coroner's pathologist, revealed no gross abnormalities except slight engorgement of the meningeal vessels. Microscopic findings* revealed diffuse areas of necrosis around the central veins of the liver, slight cloudy swelling of the renal tubular epithelium, and slight engorgement of the meningeal vessels. No Negri bodies, hemorrhages, or areas of encephalitis were noted in the brain sections. There was no evidence of foci of staphylococcal infection. It was thought that these findings were consistent with the pathologic reports of spirillary ratbite fever.

CASE 15.—A. N. (30085) a 29-year-old white woman, the mother of the patient reported in Case 14, was admitted to the surgical service on April 22, 1944. Seventeen days previously she had been bitten by a rat on the right forearm while sleeping. The wound had healed in less than one week but was slightly discolored. There was no redness or tenderness at this time. She had headaches and vertigo eight days after the bite. On the following day, a small, red "pimple" appeared on the bitten area with only slight tenderness. Each day the area seemed to become increasingly red, tender, and swollen. On the day prior to admission, red streaks were noted extending from the bitten area up the arm, and the medial aspect of the elbow became tender. On the morning of admission she applied hot packs to the area which had become black; no other treatment had been attempted.

Examination on admission revealed a well-developed and well-nourished, rational, white female whose temperature was 101.2° F. and pulse was 110. A round, black, necrotic, dry ulcer on the middle of the flexor surface of the right forearm was surrounded by a reddened, warm, indurated area. Scattered red streaks extended from this large area to the elbow and toward the axilla. The right epitrochlear gland was enlarged and tender; however, the right axillary glands were not palpable. A few scattered maculopapules were present on the forehead, cheeks, and neck.

On admission, the blood Kahn and Wassermann tests were negative. The blood count revealed the following: red cells, 4,250,000 per cubic millimeter; white cells, 11,000 per cubic millimeter; and hemoglobin, 12.6 Gm. per cent. The differential count showed 2 eosinophiles; 1 stab; and 62 segmented forms; 31 lymphocytes; and 5 monocytes. Urinalysis of an uncentrifuged specimen was essentially negative except for an occasional pus and/or epithelial cell per low-power field. Admission blood culture was sterile.

The patient's temperature fell to normal on the second day and then continued to be elevated daily between 100.4° F. and 102.2° F. for five days. On the third hospital day, the patient's blood was inoculated intraperitoneally into a mouse; examination of the peripheral blood of this animal was performed daily beginning three days later. On the eleventh hospital day, after the patient had been afebrile for five days and the primary wound had nearly healed, she was inadvertently discharged to the clinic. She returned to the clinic three days later complaining of weakness, nervousness, and increased perspiration and was treated symptomatically. On the following day *Spirillum minus* organisms were found by dark-field examination of the peripheral blood of the inoculated mouse (two weeks after inoculation). Attempts to locate this patient and have her return to the hospital were unsuccessful as she had departed for a visit in Arkansas. She went to see Dr.

*Reported by Dr. K. R. Schlademan, Pathologist, Snodgras Laboratory, St. Louis City Hospital, St. Louis, Mo.

Valentine Pardo, Monroe, Ark., on May 5, 1944 (four days after last clinic visit), at which time she had red streaks extending up her right arm, temperature of 103° F., generalized rash, and the large ulcer on the right forearm. Sulfathiazole was started in a dosage of 1 Gm. every four hours on May 5, 1944, and continued for two weeks. Neoarsphenamine, 0.6 Gm., was given intravenously on May 14, 1944, and on two later occasions at weekly intervals. Afternoon rise in temperature continued until after the second injection of the arsenical drug. One month later only a small vivid scar remained and the patient had no further complaints.*

CASE 16.—H. L. (2678) a 48-year-old white woman, was admitted to the medical service on Sept. 19, 1944. Fifteen days previously, she had received a ratbite of the left index finger which did not become infected. Five days later her left fifth finger was bitten by a rat; this area became hot, swollen, hard, and red, and remained so for thirty-six hours but gradually subsided without ulceration. On the following day, severe pain was present in the right knee, and two days later, the right ankle became painful. She came to the receiving room on Sept. 13, 1944, at which time she had a swollen right knee, tender wrists, and temperature of 104° F. The patient refused hospitalization on this day and again on the next day when her temperature was 102° F. The right wrist became markedly swollen and tender; the right hip became very painful, so that a change from sitting to standing position was very slow and painful. She had been coughing and had had anorexia since the onset of the illness. A red papular rash was present over her left arm on the day prior to entry. Fever was described as low in the morning and high at night, accompanied by severe night sweats; there had been no chills. She also had had pain and swelling of the right shoulder and elbow. Three of her children were bitten by rats during this period, but none became ill.

Blood Kahn tests on previous admissions in 1936, 1942, and 1943 had been negative.

On admission, physical examination revealed a thin, poorly nourished slightly euphoric, middle-aged white woman who appeared severely ill and who moved slowly because of acute joint pains. There was a fine, scattered, maculopapular, petechial rash over upper and lower extremities; several of the lesions were pustular. The old puncture wounds of the left index finger and hand were almost healed, and there was no lymphadenitis. The right wrist was markedly swollen, tender, hot, and red, with considerable limitation of motion because of pain. The right elbow, shoulder, and hip were very painful on motion but not noticeably swollen. There was slight swelling and tenderness of the right knee. The pharynx was slightly reddened. Scattered wheezes and coarse râles were present generally over both lung fields. The remainder of the examination was negative except for marked varicosities of both lower extremities.

Blood count on admission revealed the following: white cells, 9,700 per cubic millimeter; red cells, 3,480,000 per cubic millimeter; and hemoglobin, 10.7 Gm. per cent. A differential revealed 1 eosinophile; 2 stab and 84 segmented forms; 7 lymphocytes; and 6 monocytes. Urinalysis revealed cloudy urine; specific gravity, 1.021; sugar, negative; and albumin, faint trace. Microscopic examination of voided urine showed 6 to 8 white blood cells per high-power field. Blood Kahn test was positive (3 units), but the Wassermann test was negative.

On the day following admission, the patient's blood was inoculated on special culture media (tryptose meat infusion broth enriched with 20 per cent rabbit serum) and also intraperitoneally into two mice in amounts of 0.3 c.c. and 0.5 c.c. The mouse inoculated with 0.5 c.c. blood died in less than eight hours; death was attributed to the amount of blood inoculated. Frequent dark-field examinations of the peripheral blood of the other mouse did not reveal spirilla during the first three weeks after inoculation. This mouse lived and did not appear ill.

Aspiration of the patient's right wrist joint after the injection of sterile saline resulted in the return of a small amount of slightly cloudy fluid which was inoculated into the previously described special enriched media. A second attempt to aspirate the wrist

*Personal communication with Dr. Valentine Pardo, Monroe, Ark.

joint was made in a similar manner; however, return was clear. This fluid was inoculated intraperitoneally into two mice. Direct dark-field examinations over a three-week period did not reveal spirilla, and the mice did not develop evidence of illness.

Three cultures of the patient's blood on the special enriched media taken on the second and fourth hospital days, and incubated at 37° C. under carbon dioxide tension of approximately 8 to 10 per cent, failed to grow any organisms as did two routine blood cultures on the eighth hospital day. The *Streptobacillus moniliformis* was isolated* from the first joint culture on the second hospital day, and also on the seventh hospital day. This organism was a gram-negative, pleomorphic, chained bacillus in which occasional swollen bodies appeared among the slim bacillary bodies. The characteristic fluff-ball appearance at the bottom of the culture tubes was noted. Growth was slow and the fluff balls did not appear until after forty-eight hours.

The patient had fever during the first ten days, temperature rising to 101.6° F. on the second hospital day and to 102° F. two days later. The petechial rash disappeared on the second day. Roentgenogram of the chest revealed heavy hilar shadows with moderate increase in the peribronchial markings extending throughout both lung fields. A small fibrotic infiltration was observed in the right first interspace. Roentgenograms of the right and left wrist, elbow, shoulder, knee, and ankle joints revealed no abnormality.

Blood drawn for *Streptobacillus moniliformis* agglutination at the end of the first week in the hospital, was sent to the National Institute of Health, Bethesda, Md. Agglutination of the patient's serum against this organism occurred in a titer of 1:160 (agglutination in a dilution of 1:80 or greater is considered diagnostic of infection with this organism[9]).

On the seventh hospital day, when the results of the first joint culture were known, a second joint culture was obtained and the patient was given penicillin in a dosage of 15,000 units subcutaneously every three hours. The second joint culture subsequently grew out the streptobacillus. The next day the patient seemed somewhat improved and complained less of joint pains; however, her right wrist continued to be swollen and markedly tender, and the right knee and hip were slightly tender. Blood Kahn and Wassermann tests were positive, the total Kahn units being 40. Two days after beginning penicillin therapy, all joints seemed to be improving, the right wrist appeared much less swollen but remained tender and almost immobile, and the fever completely subsided. Two days later, the right wrist was only slightly swollen. Penicillin was continued for nine days during which the patient received 1,050,000 units. At this time, she was able to walk with ease, to flex the right wrist, to partially clench the right fist, and very little joint tenderness was present. Blood Kahn test was still positive, but the Wassermann test had become negative. The patient was discharged on Oct. 11, 1944. One month later, blood Kahn and Wassermann tests were negative. Since discharge she has remained afebrile, asymptomatic, and has gained weight during the first five months of 1945.

Table II represents a brief outline of the important clinical findings in each of the sixteen cases of ratbite fever seen in St. Louis City Hospital from 1936 through 1944. In six of these cases, the causative organism has been demonstrated: the *Spirillum minus* in five and the *Streptobacillus moniliformis* in one. Review of this table reveals that four of the sixteen cases occurred in children less than 1 year of age, three in children from 1½ to 4 years, and five later in childhood. In the five proved spirillary infections, incubation periods ranged from eight to twenty-eight days; the primary wound in three cases was inflamed, indurated, and/or ulcerated on admission. The primary wound in the other two cases had been inflamed and swollen but had healed by the time of admission. Regional lymphadenitis was present in three cases, and relapsing fever in all five cases. Blood Kahn tests were positive or doubt-

*Cultured by Mrs. Helen Doubly, Snodgras Laboratory, St. Louis City Hospital, St. Louis, Mo.

TABLE II. PATIENTS WITH RATBITE FEVER ADMITTED TO ST. LOUIS CITY HOSPITAL FROM 1936-1944

CASE	YEAR	AGE (YR.)	INCUBATION PERIOD (DAYS)	PRIMARY WOUND	REGIONAL LYMPHADENITIS	TYPE OF FEVER	RASH*	ARTHRITIS	BLOOD KAHN†	BLOOD WASSERMANN†	ETIOLOGICAL AGENT ISOLATED	COURSE‡
1 (L. N.)	1936	18	?	Healed	Yes	Relapsing	"Typical"	No	Pos.	Neg.	*S. minus*	Recovery; nephritis
2 (W. H.)	1936	1/12	28	Healed	No	Relapsing	Papulovesicular	No	Neg.	0	*S. minus*	Recovery; splenomegaly
3 (M. E.)	1936	11	2	Necrotic	Yes	Septic	Maculopapular	No	Neg.	0	None	Recovery
4 (W. P.)	1936	39	7	Indurated; ulcerated	Yes	Relapsing	Maculopapular bullar	No	Neg.	Neg.	None	Relapse; recovery
5 (L. C.)	1936	15	21	Inflamed	Yes	Relapsing	Papular	Arthralgia	Pos.	A.C.	None	Relapse; recovery
6 (L. S.)	1938	7	16	Inflamed	Yes	Irregular; relapsing	None	No	Neg.	0	*S. minus*	I & D; recovery
7 (G. O.)	1939	8	7	Indurated; ulcerated	Yes	Relapsing	None	No	Pos.	Pos.	None	Recovery
8 (E. R.)	1940	8	14	"Punched-out ulcer"	Yes	Relapsing	R.L.§	No	Pos.	Pos.	None	Splenomegaly; I & D; recovery
9 (B. D.)	1940	1½	4	Healed	No	Septic	Maculopapular	No	Neg.	0	None	Recovery
10 (G. W.)	1941	3½	7	Indurated; inflamed	Yes	?(Rapid therapy)	"Typical"	No	Pos.	Pos.	None	Herxheimer; recovery
11 (P. G.)	1942	2/12	13	Indurated; inflamed	No	?(Rapid therapy)	None	No	Neg.	Neg.	None	Recovery
12 (M. H.)	1942	4	13	Indurated; inflamed	Yes	Relapsing	"Typical"	No	Pos.	Doubt.	None	Relapse; recovery
14 (E. N.)	1944	5/12	11	Indurated	No	Relapsing	None	No	Neg.	Neg.	None	Recovery
13 (A. L.)	1942	3/12	21	Indurated; ulcerated	No	Relapsing	Papular	No	Doubt.	Doubt.	*S. minus*	Autopsy
15 (A. N.)	1944	29	8	Indurated; ulcerated	Yes	Relapsing	Maculopapular	No	Neg.	Neg.	*S. minus*	Recovery
16 (H. L.)	1944	48	1-6	Healed	No	Septic	Petechial	Yes	Pos.	Pos.	*S. moniliformis*	Recovery

*"Typical," bluish red plaques.
†Pos., positive; Neg., negative; Doubt., doubtful; A.C., anticomplementery; 0, not performed.
‡I & D, incision and drainage.
§R.L., Red lesions with white centers.

ful in two cases and negative in the other three. In the proved streptobacillary infection, the incubation period was approximately one to six days after two different ratbites. The first wound did not become infected; however, the second wound remained inflamed for thirty-six hours but was healed on admission. There was no lymphadenitis. Septic fever, petechial rash over the extremities, and arthritis of all the major joints of the right side of the body were present. Blood Kahn and Wassermann tests were positive.

Attempts were made to demonstrate the *Spirillum minus* by the mouse inoculation method in fifteen of the sixteen cases. This organism was demonstrated in the five cases by inoculation of the patient's blood into mice and microscopic examination of the peripheral blood of the mice at daily intervals using Gram, Giemsa, or Wright stains and/or dark-field illumination. In Case 1, this organism was demonstrated by Wright's stain in the peripheral blood of a mouse on the twenty-eighth day after inoculation. In Case 6, it was demonstrated on the fifteenth day after inoculation. In Case 15, dark-field examinations of the mouse's blood were unsuccessful daily from the third day until the thirteenth day when *Spirillum minus* organisms were found. In Case 14, the organisms were seen by direct dark-field examination of the lymph of the chancrelike lesion at least nine days prior to the presence of the microorganisms in the peripheral blood of mice inoculated with the patient's blood and lymph from the lesion. This is the first reported case in the United States in which the *Spirillum minus* was demonstrated in the lymph of the primary lesion and then substantiated by finding the organism by the mouse inoculation method. The presence of the streptobacillary organisms in the peripheral blood of the mouse inoculated with lymph from the fluctuant area on the left thumb cannot be adequately explained, because special cultures of the patient's blood for *Streptobacillus moniliformis* were not made. Whether this represents a pre-existing infection of the mouse with this organism or an infection produced by the inoculation of the lymph cannot be determined. This case is the second death due to ratbite fever in which the *Spirillum minus* was demonstrated by present accepted techniques; however, special cultures for *Streptobacillus moniliformis* were not employed in either case. In Case 16, the *Streptobacillus moniliformis* was demonstrated by special culture of joint fluid.

Routine blood cultures were obtained from each of the sixteen patients. The *Streptobacillus moniliformis* was not isolated in any of these cases; however, attempts to culture this organism on special media were made only in Case 16.

Arsenical drugs were used in the treatment of the first fifteen cases, whereas, penicillin was used in Case 16. Nephritis followed an acute exacerbation of spirillary ratbite fever in Case 1, which had been inadequately treated with neoarsphenamine during the first hospital admission. Splenomegaly was present in two cases. Interestingly, incision and drainage were performed in several cases without obtaining pus. A Herxheimer reaction following arsenical therapy occurred in Case 10 and consisted of fever and recurrence of the purplish macular rash.

Two patients (Cases 3 and 9) had very short incubation periods and septic fever. On admission, the wound was necrotic in Case 3 and healed in Case 9. Whether a more extensive bacteriologic study would have been successful in isolating the streptobacillus is impossible to state, but these cases resemble streptobacillary ratbite fever more than any of the other cases of unknown etiology. The other unproved cases resemble spirillary infection in regard to incubation period, wound, induration and/or ulceration, relapsing type of fever, absence of arthritis, and response to arsenicals.

TABLE III. SEROLOGIC TESTS FOR SYPHILIS IN CASES OF RATBITE FEVER

CASE	INTERVAL SINCE BITE (WEEKS)	INTERVAL SINCE ONSET (WEEKS)	KAHN TEST*	KAHN UNITS	WASSERMANN TEST*
1 (L. N.)†	12	?	4+		–
	20	?	2+		–
5 (L. C.)	3	0	–		0
	5	2	–		0
	7	4	4+		A.C.
	12	9	4+		A.C.
	18	15	1+		–
	19	16	–		0
7 (G. O.)‡	2	1	+		+
	7	6	+		+
	8	7	+		–
8 (E. R.)	8	6	+		–
	9	7	+		+
	65	63	+		–
	90	88	+		–
	108	106	–		–
10 (G. W.)‡	4½	3½	+		+
	5	4	+	160	+
	5½	4½	+	80	+
	6	5	–		–
12 (M. H.)	2	0	–		0
	3	1	–		–
	7	5	+		–
	7½	5½	+		–
	9	7	+		–
	10	8	+	4	–
	11	9	–		–
14 (E. N.)‡	1½	0	–		–
	2	½	–		–
	3	1½	–		–
	3½	2	D		D
16 (H. L.)	2	1	+	3	–
	3	2	+	40	+
	4	3	+	3	–
	12	11	–		–

*Positive, +; Negative, –; Not performed, 0; Doubtful, D; Anticomplementary, A.C.
†Kahn, negative, twelve weeks prior to bite.
‡Mother's serology negative.

From the results of the serological tests for syphilis, in Table III, several interesting facts are apparent. The blood Kahn test is more frequently positive than the Wassermann test, may become positive in as short a period as one week after the onset of ratbite fever, usually becomes positive by the fifth week of the disease (this fact was previously mentioned by Woolley[25]), and may remain positive for as long as two years after the onset of the illness. A decreasing number of Kahn units was demonstrated in Case 10, following

TABLE IVA. SUMMARY OF ALL CASES OF STREPTOBACILLARY RATBITE FEVER IN THE UNITED STATES

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	ARTHRITIS	COURSE
1	Blake[6]	1916	Mass.	67	Blood culture	Neg.	---	Autopsy
2	Litterer[26]	1917	Tenn.	14	Blood culture; agglutination	---	---	Recovery
3	Litterer[26]	1917	Tenn.	5	Blood culture; agglutination	---	---	Recovery
4	Dick and Tunnicliff[27]	1918	Ill.	10	Blood culture	Pos. (syphilis)	---	Recovery
5	Tunnicliff[11] and Mayer	1918	Ill.	1/12	Blood culture	Neg.	---	Autopsy
6	Dodd[28]	1926	Md.	10	Blood culture	Neg.	Yes	Recovery
7	Hazard and Goodkind[29]	1932	Mass.	58	Blood culture	---	Yes	Recovery
8	Scharles and Seastone[10]	1934	Mass.	Adult	Culture of joint fluid; agglutination	---	Yes	Recovery
9	Dawson and Hobby[30]	1939	N. Y.	Adult	Skin and blood culture	Pos.	Yes	Recovery
10	Dawson and Hobby[30]	1939	N. Y.	Adult	Blood culture	Pos.	Yes	Recovery
11	Farrell and associates[12]	1939	N. Y.	40	Blood culture	Neg.	Yes	Recovery
12	Allbritten and associates[23]	1940	Pa.	21	Blood culture	Neg.	Yes	Recovery
13	Hart[22]	1941	Va.	18	Agglutination; animal inoculation and culture	---	Yes	Recovery
14	Larson[31]	1941	D. C.	7/12	Blood culture	---	No	Recovery
15	Larson,[31] Brown and Nunemaker[9]	1941	D. C.	21	Agglutination	Pos.	Yes	Recovery
16	Beach and Ravenel[32]	1941	S. C.	1/12	Agglutination	Neg.	Yes	Recovery
17	Brown and Nunemaker[9]	1942	Md.	49	Blood culture; agglutination; joint fluid culture	Neg.	Yes	Recovery
18	Brown and Nunemaker[9]	1942	Md.	2/12	Blood culture; agglutination	Doubtful	No	Recovery
19	Brown and Nunemaker[9]	1942	Md.	1/12	Abscess culture; agglutination; blood culture; animal inoculation	Neg.	Yes	Recovery
20	Brown and Nunemaker[9]	1942	Md.	10/12	Agglutination	Neg.	No	Recovery
21	Brown and Nunemaker[9]	1942	Md.	1/12	Agglutination	Doubtful	No	Recovery
22	Brown and Nunemaker[9]	1942	Md.	2/12	Agglutination	Neg.	Yes	Recovery
23	Brown and Nunemaker[9]	1942	Md.	1/12	Agglutination	Neg.	Yes	Recovery
24	Witzberger and Cohen[24]	1944	N. Y.	3/12	Blood culture	Neg.	No	Recovery
25	Blake and associates[33]	1944	Conn.	73	Blood culture	---	Yes	Autopsy
26	Heilman and Herrell[34]	1944	Minn.	47	Blood culture	---	---	Recovery
27	Buddingh[35]	1944	Tenn.	59	Blood and joint fluid cultures; chick embryo inoculation	---	Yes	Recovery
28	Robins[36]	1944	Ky.	70	Blood culture; abscess culture	Neg.	No	Recovery
29	Rosen and Denzer[37]	1944	N. Y.	6/12	Blood culture; animal inoculation	Neg.	No	Recovery
30	Altemeier and associates[38]	1945	Ohio	3/12	Blood culture	---	Yes	Recovery
31	Altemeier and associates[38]	1945	Ohio	10/12	Blood culture	Neg.	No	Recovery

*Serological test for syphilis.
--- Not mentioned.

TABLE IVA.—CONT'D

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	ARTHRITIS	COURSE
32	Altemeier and associates[38]	1945	Ohio	2/12	Blood culture	Neg.	No	Recovery
33	Altemeier and associates[38]	1945	Ohio	4½	Blood culture	Neg.	Yes	Recovery
34	Wheeler[39]	1945	Mich.	Inf.	Blood culture	---	---	Death
35	Wheeler[39]	1945	Mich.	2/12	Blood culture	Neg.	Yes	Recovery
36	Wheeler[39]	1945	Mich.	1/12	Blood culture; abscess culture	---	Yes	Recovery
37	Wheeler[39]	1945	Mich.	9/12	Blood culture; mouse inoculation	Neg.	No	Recovery
38	Wheeler[39]	1945	Mich.	12/12	Blood culture	---	---	Recovery
39	Watkins	1945	Mo.	48	Joint culture; agglutination	Pos.	Yes	Recovery

neoarsphenamine therapy. An increasing number of Kahn units was demonstrated in Case 16, followed by a decreasing number following penicillin therapy.

Since Blake (1916)[6] reported the first streptobacillary case and Shattuck and Theiler (1924)[7] reported the first spirillary case in the United States, there have been a rapidly increasing number of bacteriologically proved cases. In Tables IVA and IVB, proved cases in the United States are presented according to the diagnostic method used, serology, subsequent course, and in the streptobacillary cases, the presence or absence of arthritis.

There have been thirty-nine proved cases of streptobacillary ratbite fever reported in the United States from 1916 through the first six months of 1945. Thirty-seven of these cases followed ratbite, one followed weasel-bite,[27] and the other followed trauma.[29] The streptobacillus was isolated from the blood cultures of thirty patients, two of whom had positive joint cultures,[9, 35] one had positive skin culture,[30] three had positive abscess cultures,[9, 36, 39] five had positive agglutinations,[9, 26] and three had positive animal inoculations.[9, 37, 39] Two cases, one reported by Scharles and Seastone,[10] and the streptobacillary case of the present series, were proved by positive joint fluid cultures and agglutinations. One case was proved by agglutination, animal inoculation, and blood culture of the animal.[22] The remaining six cases were established by agglutination alone.[9, 31, 32] Tileston[62] described a streptothrix present on direct dark-field examination and direct stain of the patient's blood; however, this case has not been included among the thirty-nine cases as there was no further positive bacteriologic data.

There have been forty-one bacteriologically proved cases of spirillary ratbite fever reported in the United States from 1924 through the first six months of 1945. Thirty-three cases followed ratbite, one followed mouse-bite,[49] two followed contact with dogs in a laboratory,[20] one followed cat-bite,[47] one followed cat-scratch,[53] one followed trauma to the knee without known animal contact,[53] in one there was no history of ratbite but the patient had been in a rat-infested area,[61] and one, although there was no history of ratbite, animal contact, or trauma, was diagnosed by the relapsing type of fever and by ani-

TABLE IVB. SUMMARY OF ALL CASES OF SPIRILLARY RATBITE FEVER IN THE UNITED STATES

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	COURSE
1	Shattuck and Theiler[7]	1924	Mass.	3/12	Blood inoculation into mouse and guinea pig	Neg.	Recovery
2	Dembo and associates[40]	1925	Ohio	7/12	Direct dark-field of lymph (wound)	Neg.	Recovery
3	Lawson and Lanford[41]	1925	La.	Child	Lymph into mice	---	Recovery
4	Ward[42]	1926	N. C.	3½	Direct dark-field of lymph (gland)	Pos.	Recovery
5	Zahorsky[43]	1926	Mo.	--	Direct dark-field of lymph (wound)	---	Recovery
6	Bayne-Jones[44]	1927	N. Y.	48	Skin biopsy into guinea pig	Pos.	Recovery
7	Leadingham[45]	1928	Ga.	20	Blood into mice	---	Recovery
8	Leadingham[45]	1928	Ga.	11	Blood into mice	Pos.	Recovery
9	Francis[46]	1932	Va.	6	Gland lymph into white rat	---	Recovery
10	Mock and Morrow[47]	1932	Ill.	43	Blood into guinea pig	Pos.	Recovery
11	Ripley and Van Sant[20]	1934	Ill.	26	Blood into mice, guinea pigs, and dogs	Pos.	Recovery
12	Ripley and Van Sant[20]	1934	Ill.	22	Blood into mice, guinea pigs, and dogs	Pos.	Recovery
13	Koerber[48]	1936	Calif.	12	Gland into rat; blood into guinea pig	---	Recovery
14	Reitzel and associates[49]	1936	Mass.	14	Gland and blood into mice	Neg.	Recovery
15	Woolley[50]	1935	Calif.	6½	Gland and blood into guinea pigs	Pos.	Recovery
16	Marshall[51]	1936	Ky.	2	Direct stain of lymph (wound)	Pos.	Recovery
17	Bloch and Baldock[52]	1936	Ky.	3	Blood into mice	Pos.	Recovery
18	Walker[53]	1937	Va.	16	Blood into guinea pig	Neg.	Recovery
19	Walker[53]	1937	Va.	50	Blood into guinea pig	Neg.	Recovery
20	Leadingham[54]	1938	Ga.	7	Blood into mice	Neg.	Recovery
21	Gilkey and Dennie[55]	1939	Mo.	5	Direct dark-field on lymph (wound)	Pos.	Recovery
22	Gilkey and Dennie[55]	1939	Mo.	3	Gland lymph into mouse	Neg.	Recovery
23	Woolley[25]	1939	Mass.	3/12	Blood into guinea pig	Pos.	Recovery
24	Woolley[25]	1940	Oreg.	6	Lymph into guinea pig	Pos.	Recovery
25	Greengard and Hess[56]	1941	Ill.	1/36	Blood into mice	Pos.	Autopsy
26	Packchanian and Sweet[57]	1941	D. C.	7/12	Blood into mice and guinea pigs	Neg.	Recovery
27	Larson[31]	1941	D. C.	3/12	Blood into white rats†	Neg.	Recovery
28	Rogliano[58]	1942	N. Y.	4/12	Blood into mice	Neg.	Recovery
29	Rogliano[58]	1942	N. Y.	13	Direct smear of blood; blood into mouse	Pos.	Recovery
30	Burk and Hodas[59]	1943	N. Y.	65	Direct dark-field of lymph (wound)‡	Neg.	Recovery
31	Beeson[60]	1943	Ga.		Blood into mice‡	Pos.	Recovery
32	Beeson[60]	1943	Ga.	2	Blood into mice‡	Neg.	Recovery
33	Witzberger and Cohen[24]	1944	N. Y.	59 3/12	Blood into mice and rat‡	Pos.	Recovery

TABLE IVB.—CONT'D

CASE	AUTHOR	YEAR	STATE	AGE (YR.)	DIAGNOSTIC METHOD	S.T.S.*	COURSE
34	Heilmann and Herrell[34]	1944	Minn.	7	Blood into mice	---	Recovered; arsenic; encephalitis
35	Hitzig and Liebesman[61]	1944	N. Y.	23	Special blood culture	Pos.	Autopsy
36	Wheeler[38]	1945	Mich.	3/12	Blood into mice‡	Neg.	Recovery
37	Watkins	1945	Mo.	18	Blood into mice	Pos.	Recovery
38	Watkins	1945	Mo.	4/12	Blood into mice	Neg.	Recovery
39	Watkins	1945	Mo.	7	Blood into mice	Neg.	Recovery
40	Watkins	1945	Mo.	5/12	Mouse inoculation and dark-field of lymph (wound)	Doubt.	Autopsy
41	Watkins	1945	Mo.	29	Blood into mice	Neg.	Recovery

*Serological test for syphilis.
†Agglutination (*Streptobacillus moniliformis*) negative.
‡Blood culture negative for *Streptobacillus moniliformis*.
--- Not mentioned.

mal inoculation of lymph gland.[46] Twenty-nine cases were established by animal inoculation of patient's blood, including the first six cases mentioned, not following ratbite. In the case with no history of ratbite in which the patient had lived in rat-infested areas, *S. minus organisms* were cultured by a special technique discussed later.[61] Rogliano[58] reported a diagnosis established by direct stain of the patient's blood and confirmed by animal inoculation. Four cases were diagnosed by direct dark-field examination of the lymph from the primary wound,[40, 43, 55, 59] one case was diagnosed similarly by examination of the lymph from a lymph node,[42] and one case was diagnosed by direct stain of the lymph from the wound.[51] These cases were not confirmed by animal inoculation. Case 14 of the present series was diagnosed by direct dark-field examination of the lymph from the wound, and this finding was confirmed by mouse inoculation. Three cases were established by animal inoculation of lymph gland material.[46, 48, 55] Another case was established by inoculating the material of a skin biopsy into guinea pigs and demonstrating the spirilla in the peripheral blood of the animals.[44]

Arthritis was present in twenty-one of the thirty-one cases of the streptobacillary form in which the presence or absence of arthritis was mentioned, representing 68 per cent. Walker[53] reported a case of the spirillary form in which there was arthritis, this being the only such case reported in the United States. Joint pains were present in another case, but there was no definite arthritis.[59]

There have been four deaths reported due to streptobacillary ratbite fever in the United States and the autopsy findings have been described in three of these cases. Blake[6] reported the first case in which the pathologic findings were: ulcerative endocarditis due to streptothrix (now considered the streptobacillus), subacute myocarditis, and subacute glomerular and interstitial nephritis. The second case was reported by Tunnicliff and Mayer,[11] in which there were the following pathologic findings: pallor of the viscera, broncho-

pneumonia, suprarenal hemorrhages, and hyperemia of the liver. Blake, Horstmann, and Arnold[33] in 1944, reported a case in which the anatomic diagnoses were as follows: focal myocarditis and pneumonia, and fibrous pleural and peritoneal adhesions. Wheeler[39] mentioned a case diagnosed by blood culture in which the child died of diarrhea and jaundice after having had one dose of mapharsen. No autopsy findings were mentioned. Brown and Nunemaker[9] called attention to two streptobacillary infections which had not been reported: Dr. Ruben Schulz of Boston performed the autopsy in the first case, in which the patient had endocarditis; in the second case, a patient of Dr. L. A. Krause of Baltimore, had a myocardial abscess. Sources of these infections were not mentioned.

There have been very few pathologic reports of spirillary ratbite fever. The pathologic findings in Case 14 of the present series were chiefly, central necrosis of the liver, cloudy swelling of the tubular epithelium of the kidneys, and slight engorgement of the meningeal vessels. Greengard and Hess[56] reported the clinical and pathologic summary of a 23-day-old child who developed ratbite fever and died approximately three weeks later. The *Spirillum minus* was demonstrated by the mouse inoculation method. Anatomic diagnoses were: bilateral hemorrhagic bronchopneumonia, acute serosinguineous tracheobronchitis, serofibrinous pericarditis, hemorrhagic nephritis, cloudy swelling of the myocardium, liver, and kidneys, and septic hyperplasia of the spleen. Brown and Nunemaker[9] questioned the etiology of the bronchopneumonia, and the acceptance of the spirillum as the cause of the ratbite fever since there had been no mention of the streptobacillus or streptothrix. In view of the pathologic findings, this might well represent a case of mixed streptobacillary-spirillary ratbite fever. As no attempt to culture for streptobacillus was made in Case 14 of the present series, the presence of a mixed streptobacillary-spirillary infection also cannot be excluded. Hitzig and Liebesman[61] described a case of proved spirillary infection in which an adult with no history of ratbite had positive blood Kahn and Wassermann tests, blowing systolic apical murmur, high-pitched diastolic murmur at the left of the sternum in the third intercostal space, and evidence of peripheral embolism. Repeated cultures by special technique revealed an organism resembling *Spirillum minus* in many details. Anatomic diagnoses were as follows: Subacute endocarditis of the mitral and aortic valves due to spirillum, rheumatic heart disease (chronic interstitial valvulitis of mitral and aortic valves, rheumatic myocarditis), infectious splenitis, splenomegaly, subacute splenic infarct, pulmonary congestion and edema, and chronic passive congestion of the liver. Autopsy findings of two cases reported by Japanese investigators[17] revealed the following parenchymatous changes in the organs: marked hyperemia, swelling, and degeneration of the tubular epithelium of the kidneys; degeneration, necrosis, and destruction of liver cells, particularly in the acinus centers with hyperemia and hemorrhages. There was a generalized hyperemia of the organs including the kidneys, liver, and meninges of the brain which were also edematous.

It is interesting in reviewing Table V that ratbite fever has occurred in thirty-one states and the District of Columbia, that spirillary cases have been

TABLE V. DISTRIBUTION OF RATBITE FEVER IN THE UNITED STATES

STATE	TOTAL NO. OF CASES*	PROVED CASES DUE TO S. MONILIFORMIS	PROVED CASES DUE TO S. MINUS	STATE	TOTAL NO. OF CASES	PROVED CASES DUE TO S. MONILIFORMIS	PROVED CASES DUE TO S. MINUS
1. Ala.	1	--	--	17. Neb.	2	--	--
2. Calif.	4	--	2	18. N. J.	1	--	--
3. Conn.	4	1	--	19. N. Y.	18	5	6
4. Ga.	8	--	5	20. N. C.	1	--	1
5. Ill.	17	2	4	21. N. D.	1	--	--
6. Ind.	4	--	--	22. Ohio	20	4	1
7. Iowa	4	--	--	23. Okla.	2	--	--
8. Kan.	1	--	--	24. Ore.	1	--	1
9. Ky.	6	1	2	25. Pa.	10	1	--
10. La.	6	--	1	26. S. C.	6	1	--
11. Md.	8	8	--	27. Tenn.	4	3	--
12. Mass.	6	3	3	28. Texas	2	--	--
13. Mich.	6	5	1	29. Va.	4	1	3
14. Minn.	2	1	1	30. W. Va.	5	--	--
15. Miss.	2	--	--	31. Wis.	1	--	--
16. Mo.†	22	1	8	D. C.	5	2	2
				Total	184	39	41

*Total number includes proved and unproved cases.
†Including cases reported in this paper.

reported in all regions of the United States, but that there have been as yet no reported streptobacillary cases west of Minnesota and Missouri. Foncannon[63] reported a case in Kansas in which the *Spirillum minus* was isolated by blood culture. As no further bacteriologic data were mentioned, this case was not considered a proved case in a previous review of the literature.[9]

Excellent reviews of the various diagnostic methods of isolating both organisms have been previously presented by Brown and Nunemaker,[9] and Witzberger and Cohen.[24] Chief methods of demonstrating the *Streptobacillus moniliformis*[9] as the causative organism are as follows:

1. Blood cultures
   a. Use of enriched media, such as tryptose phosphate and dextrose starch broth and agar enriched with 20 per cent serum (horse, rabbit, beef) or ascitic fluid
   b. Use of tubes with 5 to 6 c.c. of media
   c. Culture of the centrifugate of citrated blood
   d. Rapid transfer; i.e., subculture within twenty-four hours
2. Joint and abscess cultures as mentioned
3. Agglutination: titer of 1:80 or above, indicative of infection
4. Skin test with specially prepared streptobacillary antigen, producing a 1 to 3 cm. reaction when positive
5. Mouse inoculation: virulent for mice early
6. Inoculation into chick embryo, producing arthritis

Buddingh[35] recently reported on the culture by the last method and found evidence suggesting that in the initial stages, the microorganisms behaved as facultative intracellular parasites within the cytoplasm of the synovial cells.

Wheeler[39] has suggested a slightly easier culture method; i.e., inoculation of at least 8 c.c. of blood to 50 c.c. of broth routinely employed, and subculture

on chocolate agar incubating at 37° C. in a candle jar. He obtained excellent results by this technique.

The chief methods of establishing *Spirillum minus* as the causative organism are as follows:

1. Animal inoculation: dark-field examination or smear of peripheral blood of mouse, rat, or guinea pig following inoculation with:
   a. Blood
   b. Lymph node suspension
   c. Lymph from wound
2. Direct dark-field examination or smear of:
   a. Patient's blood
   b. Lymph of primary wound
   c. Lymph node suspension
3. Blood culture: special technique[61]
   a. Use 10 to 12 c.c. of 2 per cent dextrose veal infusion broth or 10 per cent tomato extract-veal infusion broth, inoculated with 3 to 5 c.c. of blood, cultured in CO_2 tension of 3.5 per cent
   b. Citrated human blood necessary for continued transplanting to eighty generations
   c. Subculture on solid media failed

Hitzig and Liebesman[61] have used this culture technique to recover the *Spirillum minus* from a case of subacute endocarditis. At necropsy, spirilla were found in vegetations on the mitral valve. In view of the fact that other culture techniques have been reported as successful,[15, 64] and then not substantiated by other workers,[8, 21] this technique will have to be evaluated by further study.

TABLE VI. SEROLOGIC TESTS FOR SYPHILIS OF PROVED CASES OF RATBITE FEVER IN THE UNITED STATES

	CASES DUE TO STREPTOBACILLUS MONILIFORMIS		CASES DUE TO SPIRILLUM MINUS	
	A. FOLLOWING RATBITE	B. FOLLOWING OTHER CAUSES	A. FOLLOWING RATBITE	B. FOLLOWING OTHER CAUSES
Total cases:	37	2	34	7
S.T.S.* stated:	25	1	28	7
S.T.S. positive:	4	1†	14	4
S.T.S. doubtful:	2	--	1	--
S.T.S. positive:	16%	--	50%	57%
S.T.S. positive (due to all causes other than syphilis):	16%		51%	

*Serologic tests for syphilis.
†Syphilitic patient.

It can be noted in the statistics of the serologic tests for syphilis in cases of "ratbite fever" in the United States, that these serologic tests are more commonly positive (false) in the spirillary than in the streptobacillary ratbite fever. Blood complement fixation tests (Wassermann), reported in fourteen cases of the streptobacillary infection, were positive in three of these cases which represents 21 per cent of the total. Blood flocculation and precipitin tests (Kahn, Kline, Eagle, Mazzini), reported in nineteen cases of this

infection, were doubtful in two cases and positive in four cases (representing 26 per cent of the total). Blood complement fixation tests (Wassermann), reported in twenty-five cases of spirillary rat-bite fever, were doubtful in one case and positive in nine cases (representing 36 per cent of the total). Blood flocculation and precipitin tests (Kahn, Kline, Hinton), reported in twenty-six cases of this infection, were doubtful in one case and positive in fourteen cases (representing 54 per cent of the total). It is apparent that the flocculation tests are more frequently positive than the complement fixation test; however, in one case, the Kahn was negative and the Wassermann was positive.[52]

Therapy in both types of ratbite fever has changed a great deal in the past few years. Arsenical injections have been used successfully in treating spirillary cases and have produced a dramatic response; however, relapses have been frequent in those cases in which less than three injections have been employed. Results of arsenical therapy have been inconclusive in streptobacillary cases; some writers have reported successes, but most cases were treated too late.[9] Brown and Nunemaker[9] employed sodium aurothiomalate in two patients, with proved streptobacillary infections, with apparently some beneficial results, for arthritis of the knee subsided following 1,000 mg. of sodium aurothiomalate administered over a period of thirteen weeks in one case, and subsided after five weeks in another case. Sulfonamide drugs have been employed without success in the treatment of streptobacillary ratbite fever.[9, 33, 36, 37]

The main factor in the great change in therapy has been the advent of penicillin. In the report of Dr. Chester Keefer,* representing the recommendation of the Office of Scientific Research and Development, and the National Research Council, penicillin therapy was stated to be of questionable value in streptobacillary ratbite fever, and was not mentioned in spirillary ratbite fever. Heilman and Herrell[34] demonstrated very effectively the value of penicillin in the treatment of both types of experimental ratbite fever. Of fifty mice infected with *Spirillum minus*, one-half were treated with penicillin and the other half remained untreated. Blood smears from the treated mice were negative from the second day until the end of one month. Blood smears from the untreated mice remained positive for one month with only one exception. Of eighty-six mice infected with *Streptobacillus moniliformis*, one-half were treated with penicillin and the other half remained untreated. Forty-two of the untreated mice died within thirty days, most dying in the first week; all of the treated mice lived and only four of the forty-three mice developed arthritis. These in vivo experiments proved the beneficial results of penicillin therapy which have been substantiated clinically in nine reported streptobacillary cases in addition to Case 16 of the present series and in one spirillary case.

Robins[36] presented the first reported case of streptobacillary infection treated with penicillin; i.e., a 70-year-old white male treated with sulfathiazole

*Report summarized in a bulletin of the War Production Board, Office of Civilian Penicillin Distribution, May 1, 1944.

unsuccessfully, having had positive cultures of the blood, bite abscesses, and secondary abscess of the leg. This patient was given 30,000 units of penicillin intravenously every morning and 15,000 units intramuscularly every three hours for three days, then 67,500 units every twenty-four hours. Five days later, fever returned, and the patient was started on the initial doses. An afebrile course followed. Total dosage of penicillin was 1,922,000 units. Arthritis had not been present. In a preliminary report of a case in Great Britain, Kane[65] described the course of a 15-year-old patient with ratbite fever treated late with penicillin. On the fiftieth day of the patient's illness, the *Streptobacillus moniliformis* isolated previously from blood culture, was found to be penicillin sensitive. After receiving 200,000 units of penicillin administered in forty-eight hours, the patient became afebrile and remained so thereafter. Altemeier and associates,[38] reported three cases of streptobacillary ratbite fever treated with penicillin. In the first case, a 10-month-old female was treated for one day with sulfathiazole; after a blood culture was positive for the streptobacillus, she was given 12,500 units of sodium penicillin intravenously every four hours for two and one-half days, then 5,000 units intramuscularly for six days, for a total of 302,500 units during eight and one-half days. Rapid recovery was noted by the disappearance of septicemia and fever. Arthritis had not been present. In the second case, a 2-month-old male had positive blood cultures on admission, but no arthritis. Penicillin was given on the third hospital day in amounts of 12,500 units intravenously or intramuscularly every four hours for the first two days, for a total of 212,500 units over four and one-half days; blood cultures became negative, patient became and remained afebrile after the third day of therapy. In the third case, a 4½-year-old female had arthritis and positive blood cultures; 4,000 units of penicillin were given intravenously every four hours for three days, then intramuscularly for two more days, 132,000 units only being available. Blood cultures became negative, rash and arthritis subsided two and five days, respectively. Recurrence occurred four days after cessation of therapy; that is, fever, rash, and positive blood cultures were present; recovery was complete two weeks later. From experience in these three cases, Altemeier and associates,[38] recommended the use of 10,000 to 15,000 units every three hours for seven days.

Wheeler[39] reported four infants with proved streptobacillary ratbite fever treated successfully with penicillin in amounts of 5,000 units every two hours. In the first case, a 7-week-old baby had arthritis of the ankles and wrists and septic fever; fever disappeared after the second day and arthritis after the fifth day of penicillin therapy. In the second case, a 5-week-old premature infant had tracheobronchitis, sternal abscess, and arthritis of tarsal-metatarsal joints which disappeared after five to seven days of penicillin therapy. In the third case, a 6-month-old Negro infant had septic fever, marked irritability, and opisthotonos; these symptoms disappeared after four to five days of penicillin therapy. In the fourth case, a 14-month-old child had fever, rash, and irritability which disappeared on the second day of penicillin therapy.

In Case 16 of the present series, 15,000 units of penicillin were given subcutaneously every three hours for a total of 1,050,000 units; the patient had an excellent recovery from a severe arthritis.

Wheeler[39] also reported the first patient with spirillary ratbite fever treated with penicillin. In this case, a 3-month-old Negro boy had high fever, a coarse macular rash over the chest, and red indurated areas on the face and scalp. Blood cultures did not grow the *Streptobacillus moniliformis;* however, *Spirillum minus* was demonstrated by the mouse inoculation method. Penicillin was administered intramuscularly in amounts of 5,000 units every three hours. Fever disappeared in less than twelve hours after penicillin therapy, and the patient was asymptomatic following five days of therapy.

These clinical reports very conclusively establish penicillin as the drug of choice in the treatment of ratbite fever. Undoubtedly some of the deaths from both types of ratbite fever could be avoided by the early use of penicillin.

SUMMARY AND CONCLUSIONS

1. Sixteen cases of ratbite fever, treated in the St. Louis City Hospital during the period from 1936 to 1944, are presented.

2. The etiological agent was demonstrated in six cases, five being due to the *Spirillum minus* and one being due to the *Streptobacillus moniliformis.*

3. The first case of ratbite fever in the United States has been reported in which the *Spirillum minus* was demonstrated in the lymph of the primary wound by direct dark-field examination and demonstrated later by mouse inoculation methods.

4. Autopsy findings of this case due to the *Spirillum minus* are presented.

5. A case of ratbite fever due to the *Streptobacillus moniliformis* successfully treated with penicillin has been presented.

6. A review of the literature has been made with regard to the symptomatology, mortality, pathology, diagnostic methods, geographical incidence, and the therapy of both types of ratbite fever.

7. Penicillin is indicated early in the treatment of either type of ratbite fever after correct diagnostic procedures have been employed.

REFERENCES

1. Wilcox, W.: Am. J. M. Sc. 26: 245, 1840.
2. Schottmüller, H.: Dermat. Wchnschr. (supplement) 58: 77, 1914.
3. Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S.: J. Exper. Med. 23: 249, 1916.
4. Levaditi, C., Nicolau, S., and Poincloux, P.: Compt. rend. Acad. d. sc. 180: 1188, 1925.
5. Robertson, A.: Ann. Trop. Med. 18: 157, 1924.
6. Blake, F. G.: J. Exper. Med. 23: 39, 1916.
7. Shattuck, G. C., and Theiler, M.: Am. J. Trop. Med. 4: 453, 1924.
8. Bayne-Jones, S.: Internat. Clin. 3: 235, 1931.
9. Brown, T. M., and Nunemaker, J. C.: Bull. Johns Hopkins Hosp. 70: 201, 1942.
10. Scharles, F. H., and Seastone, C. V.: New England J. Med. 211: 711, 1934.
11. Tunnicliff, R., and Mayer, K. M.: J. Infect. Dis. 23: 555, 1918.
12. Farrell, E., Lordi, G. H., and Vogel, J.: Arch. Int. Med. 64: 1, 1939.
13. Van Rooyen, C. E.: J. Path. & Bact. 43: 455, 1936.
14. Tunnicliff, R.: J. Infect. Dis. 19: 767, 1916.
15. Futaki, K., Takaki, I., Taniguchi, T., and Osumi, S.: J. Exper. Med. 25: 33, 1917.
16. Mooser, H.: J. Exper. Med. 39: 589, 1924.
17. Kaneko, R., and Okuda, K.: J. Exper. Med. 26: 363, 1917.
18. Ishiwara, K., Ohtawara, T., and Tamura, K.: J. Exper. Med. 25: 45, 1917.

19. Adachi, K.: J. Exper. Med. **33**: 647, 1921.
20. Ripley, H. S., and Van Sant, H. M.: J. A. M. A. **102**: 1917, 1934.
21. McDermott, E. N.: Quart. J. Med. **21**: 433, 1928.
22. Hart, A. DeV., Jr.: Virginia M. Monthly **68**: 582, 1941.
23. Allbritten, F. F., Sheely, R. F., and Jeffers, W. A.: J. A. M. A. **114**: 2360, 1940.
24. Witzberger, C. M., and Cohen, H. G.: Arch. Pediat. **61**: 123, 1944.
25. Woolley, P. V., Jr.: J. PEDIAT. **19**: 513, 1941.
26. Litterer, W.: Tr. Sect. Path. & Physiol., A. M. A.: 275, 1917.
27. Dick, G. F., and Tunnicliff, R.: J. Infect. Dis. **23**: 183, 1918.
28. Dodd, K.: Boston M. & S. J. **194**: 633, 1926.
29. Hazard, J. B., and Goodkind, R.: J. A. M. A. **99**: 534, 1932.
30. Dawson, M. H., and Hobby, G. L.: Tr. A. Am. Physicians **54**: 329, 1939.
31. Larson, C. L.: Pub. Health Rep. **56**: 1961, 1941.
32. Beach, M. W., and Ravenel, B. O.: Arch. Pediat. **58**: 685, 1941.
33. Blake, F. G., Horstmann, D. M., and Arnold, H.: Yale J. Biol. & Med. **16**: 589, 1944.
34. Heilman, F. R., and Herrell, W. C.: Proc. Staff Meet., Mayo Clin. **19**: 257, 1944.
35. Buddingh, G. J.: J. Exper. Med. **80**: 59, 1944.
36. Robins, G.: Clinics **3**: 425, 1944.
37. Rosen, E., and Denzer, D. S.: J. PEDIAT. **24**: 544, 1944.
38. Altemeier, W. A., Snyder, H., and Howe, G.: J. A. M. A. **127**: 270, 1945.
39. Wheeler, W. E.: Am. J. Dis. Child. **69**: 215, 1945.
40. Dembo, L. H., Ruh, H. O., Fargo, W. C., Taylor, G. R.: Am. J. Dis. Child. **29**: 182, 1925.
41. Lawson, E. H., and Lanford, J. A.: New Orleans M. & S. J. **77**: 349, 1925.
42. Ward, J. LaB.: South. M. J. **19**: 182, 1926.
43. Zahorsky, J.: Discussion of paper by Ward,[42] 1926.
44. Bayne-Jones, S.: N. Y. State J. Med. **27**: 1113, 1927.
45. Lendingham, R. S.: J. M. A. Georgia **17**: 16, 1928.
46. Francis, E.: Tr. A. Am. Physicians **47**: 143, 1932.
47. Mock, H. E., and Morrow, A. R.: Illinois M. J. **61**: 67, 1932.
48. Koerber, G. E.: California & West. Med. **42**: 31, 1935.
49. Reitzel, R. J., Haim, A., and Prindle, K.: J. A. M. A. **106**: 1090, 1936.
50. Woolley, P. V., Jr.: J. PEDIAT. **8**: 693, 1936.
51. Marshall, T. J.: Arch. Pediat. **53**: 664, 1936.
52. Bloch, O., Jr., and Baldock, H.: J. PEDIAT. **10**: 358, 1937.
53. Walker, H.: Virginia M. Monthly **64**: 272, 1937.
54. Lendingham, R. S.: Am. J. Clin. Path. **8**: 333, 1938.
55. Gilkey, H. M., and Dennie, C. C.: South. M. J. **32**: 1109, 1939.
56. Greengard, J., and Hess, E. R.: J. A. M. A. **116**: 2393, 1941.
57. Packchanian, A., and Sweet, L. K.: Ann. District of Columbia **10**: 95, 1941.
58. Rogliano, A. G.: Surgery **11**: 632, 1942.
59. Burk, S. B., and Hodas, J. H.: Am. J. Surg. **60**: 453, 1943.
60. Beeson, P. B.: J. A. M. A. **123**: 332, 1943.
61. Hitzig, W. M., and Liebesman, A.: Arch. Int. Med. **73**: 415, 1944.
62. Tileston, W.: J. A. M. A. **66**: 995, 1916.
63. Foncannon, F.: J. Kansas M. Soc. **31**: 331, 1930.
64. Joekes, T.: Lancet **2**: 1225, 1925.
65. Kane, F. F.: Lancet (Letters to the Editor) **2**: 548, 1944.

THE PREPARATION AND USE OF CONCENTRATED RED BLOOD CELL TRANSFUSIONS IN INFANCY

PETER G. DANIS, M.D., JACKSON K. ETO, M.D., AND JOHN S. SENNOTT, M.D.
ST. LOUIS, MO.

DURING the last few years, whole blood transfusions of fresh blood have been largely replaced in our hospital by preserved blood because of its availability.

The preparation of bank blood sometimes requires dilution. This enhances, to a degree, its use in conditions associated with any degree of hemoconcentration. However, it is at a distinct disadvantage in the very young infant and child because repeated transfusions are difficult to administer. It is at a disadvantage where one is dealing with hemolytic anemias, both acute and chronic. In order to combat these objections, we have concentrated bank blood at the time of use and have administered such blood concentrated to an even greater cell count than that of whole blood, with satisfactory results.

Pediatric patients because of their size are limited as to the volume of fluids that can be administered at any one time. In some instances the accessibility of venipunctures is an important limiting factor. Here the value of concentrated cell transfusion is obvious. Favorable results with blood concentrates on adult patients have been published by different workers who vary slightly in their method of concentrating the blood. Watson,[1] Williams and Davie,[2] and Goodall[3] have simply removed the plasma either leaving the middle layer of "gel" of white blood cells and fibrin or taking measures to exclude that layer. Murray and associates,[4] McQuaide and Mollison,[5] and Alt[6] have added solutions of either saline or glucose-saline apparently to reduce the viscosity of the cells, facilitating administration. The resultant concentrates are reported as having red blood cell counts of six million to eight million per cubic millimeter and hemoglobin content of from 17 to 20 Gm. per 100 c.c. We have concentrated red blood cells from "bank blood" which are prepared according to the method of Muether and Andrews,[7] using dextrose-citrate-buffer solution. With this, it is necessary simply to siphon off the supernatant fluid. It has been found[8] that the "gel" layer does not form in sufficient amount to require removal and the resultant concentrate has been given without any difficulty with the usual methods of intravenous administration.

PROCEDURE

Bank blood, preferably that which has been of recent preparation, is removed without shaking from the cooler. A needle is inserted in the rubber top and attached to a siphon apparatus. A second needle is placed in the top, connecting the upper part of the bottle with the outside air. The first needle is long enough to reach down to the cell layer. The supernatant fluid is then

From the Department of Pediatrics of St. Louis University.

siphoned off. Approximately 600 c.c. is removed from the bank blood mixture. That which remains in the bottle now contains a count of approximately seven to eight million red blood cells per cubic millimeter. This is then used in a routine manner of administration to the patient.

This type of blood has been administered satisfactorily without complication in ten cases of erythroblastosis fetalis, repeatedly in two cases of Cooley's anemia, repeatedly in two cases of acute hemorrhagic nephritis, in anemia of the premature infant, and in a case of cord hemorrhage and one of hemorrhage from the penis in newborn infants, which, including adults, totals 150 cases without mishap.

ADVANTAGES

Advantages of this procedure are:

1. Availability.
2. Method of preparation associated with minimum risk of contamination.
3. Minimum equipment required.
4. High cell volume, where cells are eventually needed, particularly in the newborn.

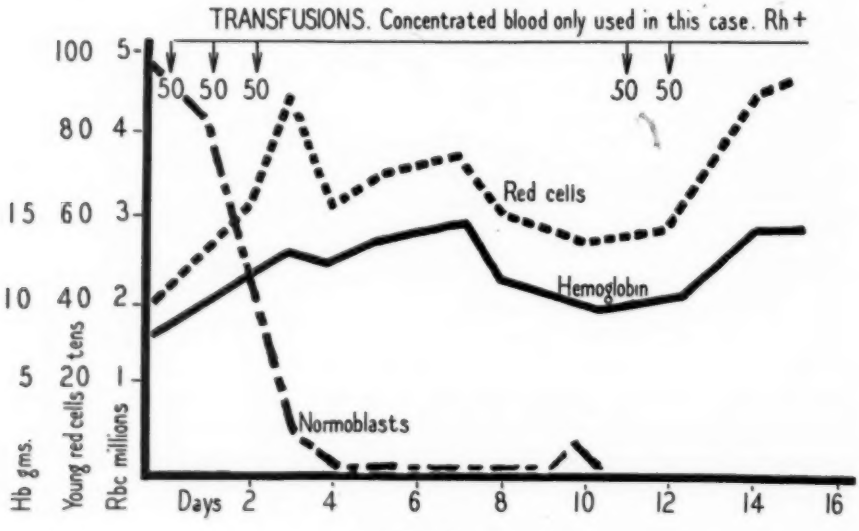


Fig. 1.

EXEMPLARY CASES

Erythroblastosis Fetalis.—The child was born jaundiced. The total white blood count twelve hours after delivery was 20,000; the total red blood count was 3,800,000. Examination of the Wright's stained blood smear showed 60 erythroblasts per 100 white blood cells counted. Mother was Rh-negative; baby was Rh-positive. Physical examination was negative except for noted icterus, splenomegaly, and hepatomegaly. Concentrated bank blood, 75 c.c., Rh-positive, was administered. Twelve hours later, the white blood count was 10,000; erythroblasts, 25 per 100 white blood cells; red blood count, 4,000,000. Twelve hours later 50 c.c. of concentrated bank blood was administered. Twelve hours later the white blood count was 9,000; erythroblasts, 10 per 100 white blood cells counted; red blood count,

4,200,000. The jaundice was at a standstill; icteric index, 100 units. Twenty-four hours later icteric index, 50; white blood count, 10,000; erythroblasts, 3 per 100 white blood cells; red blood count, 4,200,000. Three days hence there was no apparent jaundice to the naked eye; the white blood count was 9,000; erythroblasts, none seen; red blood count, 4,100,000; Weight gain was satisfactory. Result: complete regression of erythroblastosis fetalis (Fig. 1).

Cooley's Anemia.—M. S., aged 7 months, entered the hospital Sept. 1, 1943, with pallor, weakness, and vomiting of two weeks' duration. During this period she showed no weight gain. There was no diarrhea. Physical examination revealed hepatomegaly and splenomegaly. The patient was one of twins. Sibling twin died at 6 weeks. Birth history was normal. The infant was breast fed until onset of illness two weeks previously, when she was put on evaporated milk. Family history, Italian parentage. Patient had a cousin with Cooley's type of anemia which had not been benefited by a splenectomy. All relatives were dark, olive-skinned people who looked pale.

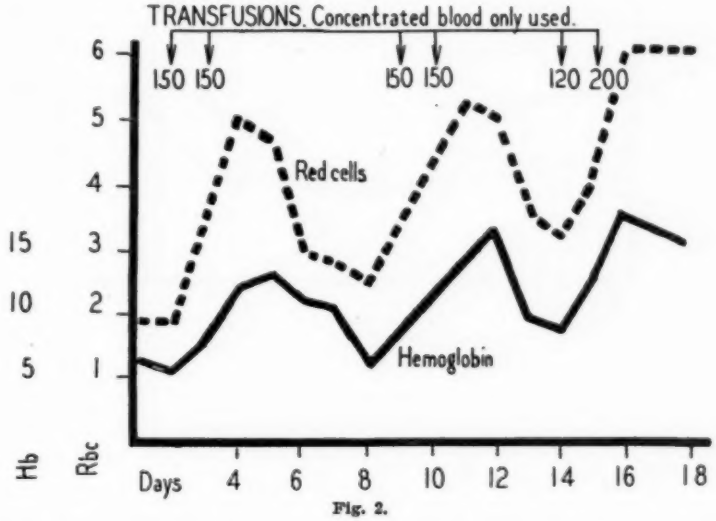


Fig. 2.

Laboratory Data and Progress.—The initial red blood count was 1,870,000; hemoglobin, 6.0 Gm.; white blood count, 21,000; normoblasts, 18 per 100 white blood cells on Wright's stained blood smear; hematocrit, 16 volume per cent; cell fragility test with saline, 0.38 to 0.22; mean corpuscular volume, 89.5; mean corpuscular hemoglobin, 33; mean corpuscular hemoglobin concentration, 37 per cent. Study of stained smear revealed polychromatophilia, achromia, anisocytosis, and poikilocytosis. Concentrated cells, 150 c.c., were given two days after the laboratory work was done. Following this, the red blood cell count was 3,370,000; hemoglobin, 8.0 Gm.; hematocrit, 22 volume per cent; normoblasts, 11 per cent. On the third day, 150 c.c. of concentrated cells were given. Following this, the red blood count was 5,100,000; hemoglobin, 12.0 Gm.; hematocrit, 32 volume per cent. By the twelfth day, the red blood count had gradually fallen to 2,650,000; hemoglobin, 6.0 Gm.; normoblasts, 6 per cent. Concentrated blood, 150 c.c., was given the thirteenth and fourteenth days. Following this, the red blood count was 5,580,000; hemoglobin, 15.0 Gm. On the eighteenth day, the red blood count had dropped to 3,260,000. Concentrated blood, 150 c.c., again was given daily for two days. Following this, the red blood count rose to 6,130,000; hemoglobin, 15.0 Gm. Patient was discharged. Since then, the patient has been in and out of the hospital for transfusions. Anemia invariably has returned over varying periods of time. Thus far, the response to transfusion has been only transitory (Fig. 2).

Anemia of the Premature.—The patient, a boy, was one of twins. Premature birth occurred at six months' gestation. Birth weight was 2 pounds, 11 ounces. Delivery was not difficult. The respiration and cry were spontaneous though sluggish. He was put on Olac formula and did well for one and one-half months. He then developed pallor and his weight gain became less progressive. The red blood count was 2,800,000; hemoglobin, 9.0 Gm. The patient was transfused with concentrated cells, 30 c.c., on two successive days. The red blood count rose to 5,500,000; hemoglobin, 14.0 Gm. The patient's color improved and weight gain became normal. Eight months later the baby showed continued weight gain, and the red cell count was 4,200,000 with a hemoglobin of 10.0 grams. Follow-up revealed no anemia; no transfusion reactions (Fig. 3).

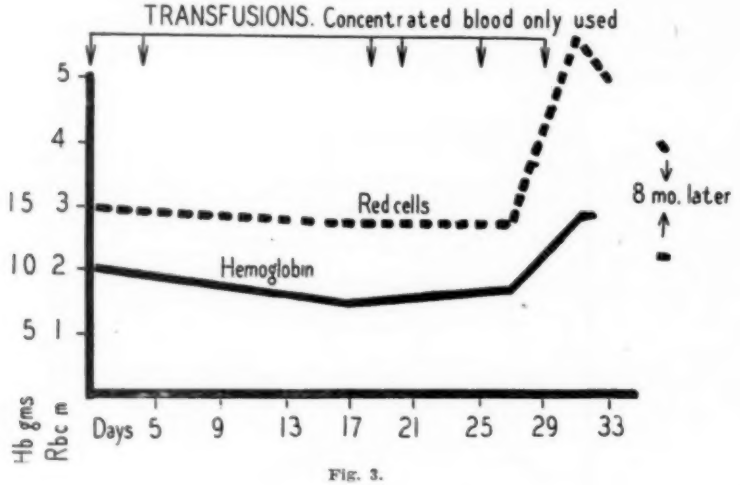


Fig. 3.

INDICATIONS

1. Hemolytic anemias
   a. Lederer's acute
   b. Erythroblastosis fetalis
   c. Cooley's
   d. Target cell
   e. Familial hemolytic
   f. Sickle cell icterus
   g. Macrocytic
   h. Acquired
      (1) Poisoning
      (2) Infection
2. Aplastic anemia
   a. Infectious
   b. Constitutional
3. Von Jaksch
4. Anemia of the premature
5. Severe nutritional
6. Hemophilia
7. Thrombopenic purpura
8. Hemorrhagic disease of the newborn
9. Hemorrhagic nephritis
10. Traumatic hemorrhage
    a. Newborn infant
       (1) Cord
       (2) Circumcision
       (3) Liver
    b. Child
       (1) Rupture of spleen
       (2) Post tonsillectomy
11. Rheumatic fever

REFERENCES

1. Watson, L.: Lancet **1**: 107, 1943.
2. Williams, G. E. O., and Davie, T. B.: Brit. M. J. **2**: 641, 1941.
3. Goodall, A.: Glasgow M. J. **141**: 161, 1944.
4. Murray, C. K., Hale, D. E., and Sharr, C. M.: J. A. M. A. **122**: 1065, 1943.
5. McQuaide, D., and Mollison, P. L.: Brit. M. J. **11**: 555, 1940.
6. Alt, H. L.: J. A. M. A. **122**: 417, 1943.
7. Muether, R. O., Andrews, K. R.: Am. J. Clin. Path. **11**: 307, 1940.
8. Muether, R. O.: South. M. J. **38**: 330, 1945.

AN EVALUATION OF THE DISTINCTION IN THE CLINICAL COURSE AND THE TREATMENT OF ERYTHROBLASTOSIS AND ICTERUS GRAVIS

PETER G. DANIS, M.D.
ST. LOUIS, MO.

FOR many years two separate entities seen in newborn infants were described. Both were usually fatal. Both were associated with a hemolytic anemia. One was known as icterus gravis. The other was called erythroblastosis fetalis. Diamond and associates[1] in 1932, associated these two diseases in twins and in families so extensively that they concluded that these diseases, as well as hydrops and "anemia of the newborn," were varying stages of the same disease. In 1940 Levine and Katzin[2] demonstrated a relationship between the Rh factor and erythroblastosis fetalis. This bore out Darrow's[3] theory of the possible cause of the syndrome. Since then, many controveries have arisen because of different conceptions or understandings of the disease.

Clinicians have made their own decisions in their studies, mostly on a basis of severity, as to which cases might be included in any study of the disease, often disregarding the studies of Diamond and associates,[1] which were by far the most accepted at the time that the Rh factor was introduced to medicine. Pathologists[4, 5] have set up standard requisites for the diagnosis of erythroblastosis fetalis, standards which other pathologists[5, 6] have used to limit Rh-negative incompatible as the etiology. The result has been varying, credit frequently being given to the Rh factor clinically as the sole etiology of the disease. Since the printed word backed by extensive material has been the accepted authority in medicine to date, we[7] investigated a group of cases, all of which would well fall into the classification of Diamond and associates,[1] and found only 67 per cent of the cases could be demonstrated to have the Rh-negative setup. For this, our work has been questioned by a pathologist[8] with a different set of rules for inclusion or exclusion of cases in this syndrome, in spite of the fact that pathologists[6] constantly bring out pathological findings in newborn infants of erythroblastic excess in the liver and other conditions, which are in no way related to this disease.

It is, therefore, worthy of point today for the benefit of the physician who sees the living patient to give a description of the following two strikingly different syndromes seen in the newborn, which in the majority of cases bear up the Rh syndrome but whose courses, and particularly the treatment and outcome, vary distinctly; two clinical syndromes, which, if proved to be different diseases, would clear up a greatly muddled subject and would go far in truly evaluating the role of the Rh factor.

TYPE I

At birth or in the first day of life, an obvious jaundice develops in the newborn. Some edema is present occasionally and in this case, too, there is a

From the Department of Pediatrics of St. Louis University.

conspicuous paleness to the baby. But far more commonly associated with the jaundice are petechiae of varying size. Because of these observations, blood counts are obtained. There is found a varying degree of anemia associated with a marked erythroblastosis. A history is presented of previous jaundiced babies in the family or of previous deaths of newborn babies in the family involving very seldom, however, the first born. If left untreated, the baby becomes more jaundiced, very toxic, more anemic, and death ensues in about three days. His nutrition is either normal or poor. When treated with blood transfusions within the twenty-four hours in sufficient amounts, there is very marked improvement in the blood picture. The number of erythroblasts drops and the red count drop slows up. Repeated transfusions continue to control and improve the blood picture but the jaundice markedly increases for three or four days; during this time the stool, which has been dark, becomes lighter in color. More petechiae occur, and the prothrombin time increases.

TYPE II

The second syndrome starts differently. This baby is born an exceptionally well-nourished baby. His color is good and during the first twenty-four hours, there are no alarming findings. However, in the second twenty-four hours, the baby rapidly becomes jaundiced; by the third day, the jaundice is extreme and there is very frequently, to a greater or lesser degree, retraction of the baby's neck. Examination reveals a normal blood count or a mild anemia with but a few erythroblasts. The baby develops from this point a gradual anemia which, if sufficiently neglected, will be associated with a definite erythroblastosis after it drops below three million. The spleen becomes enlarged and the prothrombin time remains high regardless of the administration of vitamin K. Throughout, nutrition is rarely a problem. The spinal fluid is high in bile pigment. The immediate outlook in these cases is good but, unfortunately, the final outlook is poor. The evidence of brain damage from the irritation of bile pigment results in a residual very much as that seen in the well-known spastic. Hemorrhage of any sort is rare in these babies, in spite of the high prothrombin time.

In Type I the meningismus has not been seen by us. The anemia develops more rapidly; enlargement of the spleen is often present at birth; and the hemorrhagic tendency is greater.

These distinctions are very important to the clinician treating the newborn infant.

In the first disease transfusions are needed immediately, preferably of concentrated blood cells, typed and matched.

In the second condition the value of blood given immediately is debatable. It may not be needed because of obvious lack of marked anemia. However, its elements may materially stop the obvious hemolytic process. It therefore should be given in smaller amounts than in the first type or it may contribute to the total excess of bile pigment in the circulation. What is extremely more important is to attempt to protect and stimulate an inefficient liver. Therefore, the use of glucose subcutaneously early and repeatedly, and the administration of choline

chloride[9] from birth is of extreme importance to prevent the fatty degeneration.[9, 10] No doubt, many other clinical findings should be listed, but those given suffice to demonstrate the clinical difference as seen by the pediatrician.

It is our belief because of the present emphasis on our transfusion therapy of "select" bloods that the clinical distinction given here deserves restitution regardless of the classification of Diamond and associates of the two conditions being one and the same, and regardless of whether the Rh-negative factor is the cause in 50, 75, or 90 per cent of the cases.

CASE REPORTS

Example of Type I

Baby S.—At birth, June, 1943, the baby weighed 7 pounds, 2 ounces. The cry was spontaneous; there were no anomalies; vernix was yellow tinged; there was edema of the scrotum.

Three hours after birth there were petechiae on the thighs and arms. Examination of the blood revealed a red blood count of 3,700,000; white blood count corrected, 10,000; erythroblasts, 350 per 100 white blood cells found in stained blood smear.

Eight hours after birth the baby was transfused with 75 c.c. of concentrated blood cells.

Sixteen hours later the red blood count was 3,400,000. The baby was markedly jaundiced. The blood transfusion was repeated.

Twenty-four hours later (baby 48 hours old) the red blood count was 3,400,000; hemoglobin, 70 per cent; icteric index, 90; erythroblast count, 100 per 100 white blood cells.

On the fourth day the red blood count was 3,300,000; hemoglobin, 70 per cent; erythroblasts, 50 per 100 white blood cells. The baby was still toxic, jaundiced with more greenish tinge, eating poorly. Concentrated blood cell transfusion, 100 c.c., was given.

On the fifth day the red blood count was 4,000,000; hemoglobin, 82 per cent; erythroblasts, 10 per 100 white blood cells.

On the sixth day the red blood count was 4,100,000; hemoglobin, 80 per cent.

On the eighth day the red blood count was 4,000,000; hemoglobin, 80 per cent; icteric index, 70. The baby was eating better.

On the thirteenth day, the red blood count was 3,800,000; hemoglobin, 80 per cent, icteric index, 50. The baby was gaining weight.

On the twentieth day, the red blood count was 3,300,000; hemoglobin, 65 per cent; icteric index, 30. The baby was gaining slowly. Blood, 70 c.c., was given by transfusion.

On the twenty-third day, the red blood count was 4,000,000; hemoglobin, 75 per cent.

Thereafter, the jaundice became undetectable. Iron administration was necessary about one month later because of a fall in hemoglobin. Otherwise, no further specific care was needed.

During the entire time, the baby received 10 grains of choline chloride daily and subcutaneous glucose daily for the first ten days of life.

Family History: There were two previous births with both children living and well. There was no history of jaundice. The mother showed strong Rh antibodies titer. The mother was Rh negative; the father, Rh positive; the baby, Rh positive.

Example of Type II

Baby J.—At birth, Oct. 10, 1944, the baby weighed 7 pounds, 10 ounces. The cry was spontaneous. There were no anomalies or other pathologic physical findings.

Twenty-four hours after birth, there was definite yellow discoloration of the skin.

Forty-eight hours after birth, the red blood count was 4,600,000; hemoglobin, 100 per cent; erythroblasts, 5 per 100 white blood cells; white blood count corrected, 12,000.

On the third day of life, the jaundice was extreme. The icteric index was not accurately estimable. The baby was drowsy but accepted food. Weight gain of one ounce occurred from the previous day. The diapers were deeply stained. The head was slightly retracted with

no bulging of the fontannel. The red blood count was 4,100,000; hemoglobin, 80 per cent; erythroblasts, 5 per 100 white blood cells. Subcutaneous glucose was given three times a day.

On the fourth day, the red blood count was 4,000,000; hemoglobin, 75 per cent.

On the fifth day, the red blood count was 3,700,000; hemoglobin, 65 per cent. The jaundice was extreme. The head was still retracted. Spinal puncture revealed no appreciable red blood cells but was heavily bile stained. The blood culture was negative; blood Wassermann was negative. Stools were yellow. Matched blood, 50 c.c., was given by transfusion.

On the sixth day, the red blood count was 3,900,000; hemoglobin, 70 per cent. The jaundice was detectably less. The neck was not quite as stiff. The stools were paler in color. The nutrition was good.

On the tenth day, the baby was still markedly jaundiced. The neck, however, was more relaxed; the stools were darker in color; and the red blood count was 3,400,000; the hemoglobin, 60 per cent.

On the twelfth day, the red blood count was 3,000,000; icteric index, 70. The spleen was palpable. The baby was more alert. Blood, 75 c.c., was administered.

During the entire time the baby received subcutaneous glucose daily and choline chloride, grains 10, daily. The jaundice remained in some degree until the baby was 1 month of age. At this time a third transfusion seemed advisable since the hemoglobin had fallen to 55 per cent and the red blood count to 2,900,000. Following this, recovery was uneventful, but the child's neuromuscular development was slower than average.

Family History: Two living and well children; two children dead, one of whom died immediately following birth, supposedly with edema.

REFERENCES

1. Diamond, L. K., Blackfan, K. D., and Baty, J. M.: J. PEDIAT. **1**: 269, 1932.
2. Levine, P., and Katzin, E. M.: Proc. Soc. Exper. Biol. & Med. **45**: 343, 1940.
3. Darrow, R. R.: Arch. Path. **25**: 378, 1938.
4. Rautmann, H.: Beit. z. path. Anat. u. z. Allg. Path. **54**: 332, 1912.
5. Macklin, M. T.: Am. J. Dis. Child. **53**: 1245, 1937.
6. Macklin, M. T.: J. PEDIAT. **25**: 533, 1944.
7. Danis, P. G., Gallagher, F. W., and Jones, L. R.: J. PEDIAT. **22**: 171, 1943.
8. Potter, E. L.: Am. J. Dis. Child. **68**: 32, 1944.
9. Danis, P. G., and Anderson, W. A. D.: South. M. J. **35**: 1070, 1942.
10. Klemperer, P.: Am. J. Dis. Child. **28**: 212, 1924.

THE USE OF RH-POSITIVE BLOOD CELLS IN THE TREATMENT OF ERYTHROBLASTOSIS FETALIS

PETER G. DANIS, M.D., JACKSON K. ETO, M.D., AND JOHN S. SENNOTT, M.D.
ST. LOUIS, MO.

WITH our present knowledge, erythroblastosis fetalis may be said to be a disease of two phases. First, acute hemolytic anemia, and second, liver dysfunction. Any acute hemolytic anemia needs red blood cells in large quantities quickly. With the development of the scalp vein technique for transfusing infants, the mortality rate of this disease began to drop. However, recognition of the mechanism back of the hemolysis has caused great concern over the selection of the *type* of blood for transfusion.

Soon after the original publication of Levine and Katzin[1] in regard to the Rh factor in this disease, we were fortunate in obtaining from a mother of a baby with erythroblastosis a very potent anti-Rh serum. With this serum and the cooperation of all of the hospitals in St. Louis, we had the opportunity of examining the blood and treating a proportionately large group of cases of hemolytic anemia of the newborn with severe icterus. We found during this study[2] that the identification of Rh type accordingly required particular technique which at that time fortunately was available to us at St. Louis University. At that particular time, Dr. Gallagher examined the blood of the freshman and sophomore medical school classes and obtained five Rh-negative donors. The blood of these men was administered in a number of cases of erythroblastosis. Clinically, the results were not any more impressive than when we used Rh-positive blood. However, recent articles by Weiner[3] have given great import to the use of Rh-negative blood as a treatment of the infant with erythroblastosis fetalis. On the other hand, to evaluate comparatively the use of Rh-positive blood (which is always more readily available) is still the interest of the authors.

The following factors influenced our thinking:

1. Rh-negative blood for transfusion is not universally readily available.

2. We have never felt that Rh studies on blood, up to the present time at least, were too reliable when done rapidly in the hospital, and since the bacteriology department of the University cannot do them on demand, we have not had them available when most needed.

3. We were impressed repeatedly with the results obtained with father's blood. One case was previously reported in an article on the treatment of the disease with choline chloride in the *Southern Medical Journal*.[4] In many cases in which the obstetrician had given one transfusion of father's blood before the patient was seen by us, the result was quite remarkable.

From the Department of Pediatrics of St. Louis University.

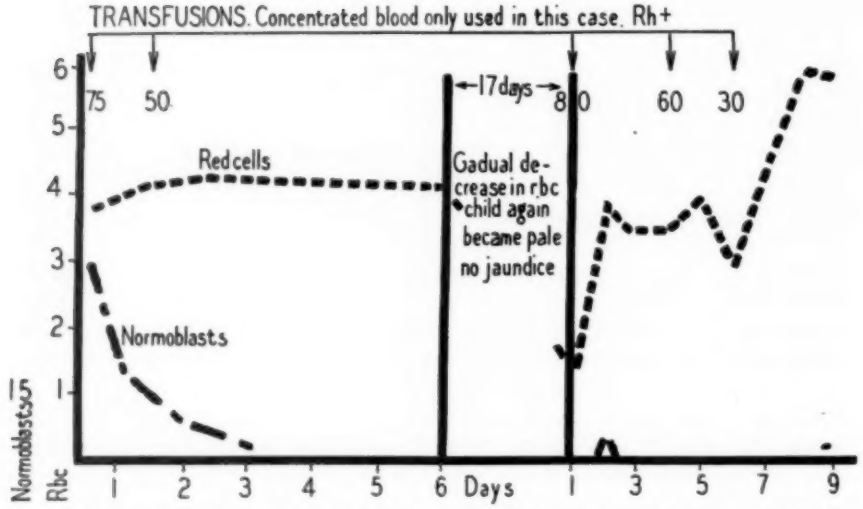


Fig. 1.—Case 1. Pale at birth. Jaundice appeared in twenty-four hours, persisted for ten days. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

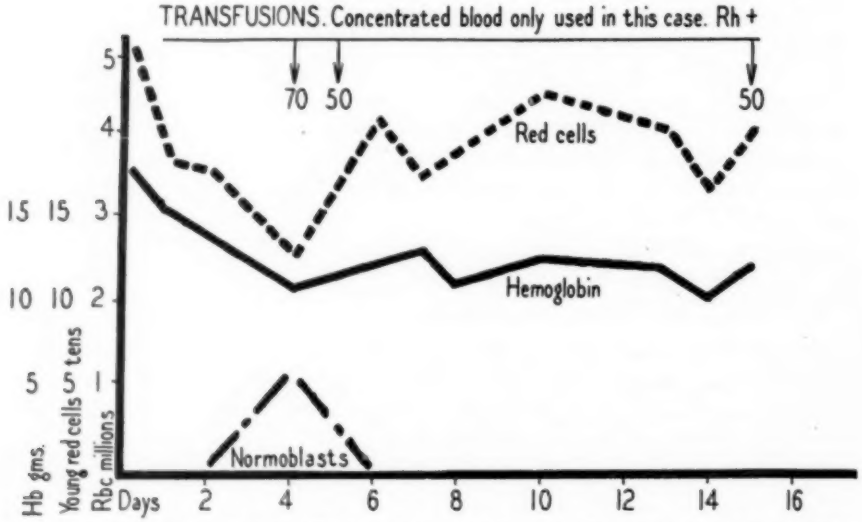


Fig. 2.—Case 2. Not jaundiced or pale at birth. Jaundice appeared in twenty-four hours and persisted for ten days. Pale twenty-four hours after birth. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

4. If one accepts Diamond, Blackfan, and Baty's[5] broad classification of this syndrome, one finds many cases in which the baby's mother is not Rh-negative. This we have observed and reported.[2]

5. We have not been impressed with the results of our original administration of Rh-negative cells. The erythroblast count was slow in dropping.

6. Our thought has been as follows: The baby's blood in the vast majority of incidences of erythroblastosis is Rh positive. This blood is therefore susceptible to the Rh antibody. This Rh antibody is limited in amount in the baby for it has been passively received from the mother, from whom all connection has been severed at the time of birth. (Breast feeding is contraindicated.[6])

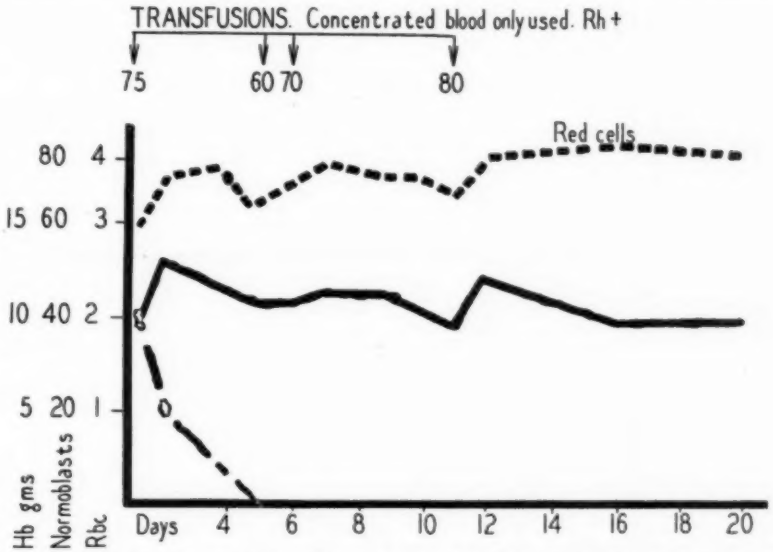


Fig. 3.—Case 4. Jaundiced twenty-four hours after birth; jaundice persisted for eight days. Mother's blood, Rh negative, baby's blood, Rh positive. Two weeks later red blood count, 2.90. Concentrated blood, 110 c.c. Count, 4.20. No subsequent anemia. No transfusion reactions.

This antibody eventually is completely absorbed by the baby's red blood cells. This produces an extreme strain on the baby's blood-forming organs, one which may be reflected by hemopoietic exhaustion for an indefinite time. This is the only thing that can happen when Rh-negative blood is used as a means of treatment since its very meaning implies its noninterference with the activity of the Rh antibody. If Rh-positive cells are used, some of the Rh antibody is absorbed by this artificially donated antigen. The massive damage to the baby's own cells is reduced, the reduction depending on the amount and the rapidity of administration of the Rh-positive cells. True, there would be destruction, as a result of the administration of all these Rh-positive cells. The total destruction of cells could not be greater in the one instance over the other. Therefore, the damaging effect on the liver of massive blood destruction could not be greater when artificially supplied Rh-positive cells are used than when only the baby's

Rh-positive cells are destroyed, and the massive damage to the baby's own cells could not help but be reduced. If the antibody is specific for the baby's cells, then the Rh-positive blood we administer like Rh-negative blood cells will be equally usable by the baby. We do not know the whole mechanism of Rh-positiveness of red blood cells, and consequently it seems rational to give the baby

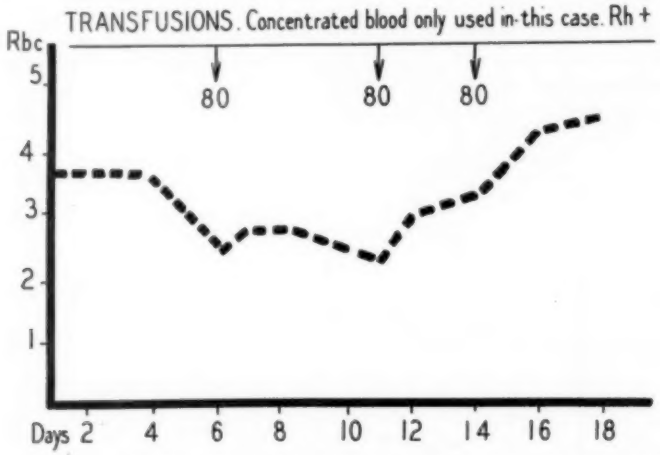


Fig. 4.—Case 5. Jaundiced twenty-four hours after birth. Jaundice persisted for eleven days. Mother's blood, Rh negative. Baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

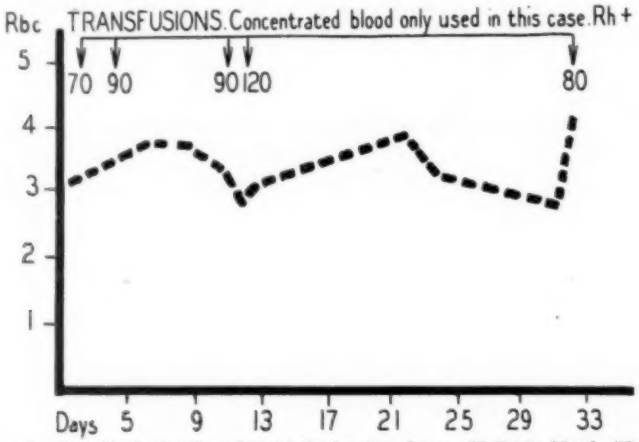


Fig. 5.—Case 6. Jaundiced shortly after birth for ten days. Mother's blood, Rh negative; baby's blood, Rh positive. Follow-up reveals no anemia. No transfusion reactions.

blood which is identical with his own, since 85 per cent of all persons' blood is Rh positive. Since the incidence of this disease is being more frequently recognized, we feel it important to call attention to these facts, since the literature today would imply that the use of Rh-positive blood for these babies is contraindicated.

Again, since we are dealing with an acute hemolytic anemia, the concentration of red blood cells in the transfusing fluid is of great importance.

The accompanying graphs (Figs. 1 to 5) demonstrate the response of a typical case to Rh-positive concentrated cell transfusion. When a blood count of over 4,000,000 and a hemoglobin of 85 per cent were maintained, no further transfusions were administered. If, however, a drop was observed or the number of erythroblasts increased, blood was again administered.

We conclude:

That Rh-positive blood can very satisfactorily be used to treat erythroblastosis fetalis.

That concentration of the red blood cells reduces the frequency and the volume of transfusions necessary.

That concentration can be simply obtained by syphoning off the plasma down to a centimeter[7] of the cell level in refrigerated blood.

That such cell concentrations do not require any different method of administration or preparation for use.

That such transfusions do not produce any clinical evidence to contraindicate their use.

All babies with this disease, in our opinion, have either primary or secondary liver dysfunction.[4] Glucose is therefore an indicated adjunct to treatment. Choline chloride, which supplies, according to our knowledge today, the CH_3 radical for fat mobilization, is particularly valuable in preventing the fatty degeneration consistently found in post-mortem examinations in this disease. It is our opinion that it should be used constantly throughout the course of the disease.

REFERENCES

1. Levine, P., and Katzin, E. M.: Proc. Soc. Exper. Biol. & Med. **45**: 343, 1940.
2. Danis, P. G., Gallagher, F. W., and Jones, L. R.: J. PEDIAT. **22**: 171, 1943.
3. Weiner, A. S.: Arch. Path. **32**: 227, 1941.
4. Danis, P. G., Anderson, W. A. D.: South. M. J. **35**: 1070, 1942.
5. Diamond, L. K., Blackfan, K. D., and Baty, J. M.: J. PEDIAT. **1**: 269, 1932.
6. Witebsky, E., Anderson, G. W., and Heide, A.: Proc. Soc. Exper. Biol. & Med. **49**: 179, 1942.
7. Muether, R. O.: South. M. J. **38**: 330, 1945.

APPRAISAL OF TREATMENT OF HEMOPHILUS INFLUENZAE TYPE B MENINGITIS WITH SPECIFIC RABBIT SERUM AND SULFONAMIDES

Based on Observation of Sixty Cases

Albert M. Edmonds, M.D., and Erwin Neter, M.D.
Buffalo, N. Y.

IN SPITE of the fact that since the advent of type-specific rabbit serum and sulfonamides, the prognosis in meningitis due to *Hemophilus influenzae* has radically changed, many pertinent problems still remain to be solved. For instance, the case fatality rate in infants continues to be relatively high; the value of intrathecally injected serum is still a moot question; little is known with respect to measures that prevent complications and sequelae; it is as yet difficult, if not impossible, to determine in advance the minimal and optimal amounts of antiserum and sulfonamides required to eliminate the organisms; and, finally, tests are not available which permit an appraisal of the virulence of the infecting bacillus. So many factors influence the outcome of the disease that it becomes rather difficult to evaluate the results obtained with certain therapeutic methods. This is well brought out by the fact that the reported case fatality rates in patients treated with type-specific serum and sulfonamides vary from less than 20 per cent up to 50 per cent (Table I).

A relatively large number of patients suffering from this disease were treated at this hospital with Alexander's type-specific serum and various sulfonamide compounds. In order to obtain additional information on the value and particularly the shortcomings of this form of specific therapy, the beneficial and adverse effects resulting from intrathecally injected antiserum, and the incidence of complications and sequelae, these cases were utilized for analysis. The data obtained are incorporated in this report.

This series is comprised of sixty consecutive cases of bacteriologically proved meningitis due to *H. influenzae* type B, treated with serum and sulfonamides. It is divided into two groups for the reason that the case fatality rate in patients treated until Sept. 30, 1944, was considerably higher than that of patients observed until May 31, 1945. The possibility presented itself that a comparison of the two groups might yield information leading to a better management of this malady.

As an index of the type of case and severity of the infection at the time therapeutic measures were instituted, it will be helpful to discuss briefly the age distribution of the patients, the incidence of bacteriemia and the spinal fluid glucose levels prior to therapy.

Tables II and III show the age distribution of the patients of both groups and the incidence of bacteriemia in fifty cases. It is worthy of note that *H.*

From the Departments of Pediatrics and Bacteriology of the University of Buffalo, School of Medicine, and the Children's Hospital.

TABLE I. CASE FATALITY RATES OF PATIENTS WITH H. INFLUENZAE MENINGITIS TREATED WITH TYPE-SPECIFIC RABBIT SERUM AND SULFONAMIDES

AUTHORS	NUMBER OF CASES	NUMBER OF DEATHS	CASE FATALITY RATE (%)
Alexander[1]	87	19	22.0
Turner[2]	20	10	50.0
Comly and McKee[3]	6	1	16.8
Birdsong, Waddell, and Whitehead[4]	8	1	12.5
Boisvert, Fousek, and Grossman[5]	26	4	15.4
Scully and Menten[6]	9	4	44.0
Neter[7]	7	3	42.9
Edmonds and Neter	60	20	33.0
Silverthorne[8]	16	8	50.0
Smith et al.	28	2	7.0
Total	267	72	29.36

TABLE II. NUMBER OF FATALITIES AND RECOVERIES IN SIXTY CASES OF H. INFLUENZAE MENINGITIS

	AGES						
	0-3 MONTHS	3-6 MONTHS	6-12 MONTHS	1-2 YEARS	2-5 YEARS	5 YEARS AND OVER	TOTAL
Group I							
Recoveries	0	0	3	8	13	3	27
Fatalities	1	2	8	3	2	1	17
Group II							
Recoveries	0	1	3	4	4	1	13
Fatalities	1	1	0	0	1	0	3
Total							
Recoveries	0	1	6	12	17	4	40
Fatalities	2	3	8	3	3	1	20

TABLE III. BLOOD CULTURE IN H. INFLUENZAE MENINGITIS

	NUMBER OF PATIENTS WITH POSITIVE BLOOD CULTURES	NUMBER OF PATIENTS WITH NEGATIVE BLOOD CULTURES
Group I		
0-12 months of age	10 } 26	1 } 8
1 year and over	16 }	7 }
Group II		
0-12 months of age	5 } 13	1 } 3
1 year and over	8 }	2 }
Total		
0-12 months of age	15 } 39	2 } 11
1 year and over	24 }	9 }

TABLE IV. SPINAL FLUID GLUCOSE IN H. INFLUENZAE MENINGITIS

	GLUCOSE VALUES UP TO 20 MG. %	GLUCOSE VALUES OF 20 MG. % AND OVER
Group I		
Recoveries	13 } 25	5 } 9
Fatalities	12 }	4 }
Group II		
Recoveries	7 } 9	6 } 7
Fatalities	2 }	1 }
Total		
Recoveries	20 } 34	11 } 16
Fatalities	14 }	5 }

influenzae was found in the blood in 78 per cent of the patients and that bacteriemia was somewhat more frequently present in infants than in older children. It is also evident that no striking differences exist between the two groups. The spinal fluid glucose levels prior to commencement of specific therapy were determined in fifty instances. The results are summarized in Table IV. It may be seen that values of less than 20 mg. per cent were encountered in relatively more patients of Group I than of Group II.

All patients received anti-*H. influenzae* type B rabbit serum (Squibb) intravenously, as well as one or more of various sulfonamide compounds. Twenty patients were given, in addition, antiserum intrathecally. The attempt was made throughout to administer intravenously adequate amounts of serum to maintain freely circulating antibodies in the blood and to procure sterilization of the cerebrospinal fluid.

Of the sixty cases treated, forty recovered from the infection and twenty succumbed. The case fatality rate, therefore, was 33⅓ per cent (Table I). If patients who died within less than twenty-four hours after commencement of specific therapy are excluded, the corrected case fatality rate is 28½ per cent. Among the twenty fatalities is one patient who probably recovered from the meningitis but died from a late complication, pneumonia, after hospitalization for two and one-half months. Post-mortem examination was not performed. As may be seen from Table I, the case fatality rates in Groups I and II were 38.7 per cent, and 18.7 per cent, respectively. Thus it appears that the treatment was more nearly successful in patients of Group II than of Group I. The question arises, however, whether this striking difference in the case fatality rates is due to variations in the management of specific therapy or to differences in the disease itself. Aside from the fact that spinal fluid glucose levels below 20 mg. per cent were found somewhat more often in patients of Group I than of Group II, no evidence of differences in the severity of the infection per se between the groups has been brought to light. It is quite possible that more intensive follow-up studies and therapy may be the reason for the lower case fatality rate in Group II.

From a clinical point of view, it is equally as important to consider the end results as it is the fatality rate. Aside from a complete check-up at the time of discharge from the hospital, a follow-up inquiry was made at the time of writing on all patients with residual lesions. Among the twenty-seven patients of Group I who recovered from the infection, twenty-three can be considered physically and mentally normal. Nine of the thirteen surviving patients of Group II made a complete recovery. Therefore, as far as complete recovery is concerned, the results accomplished in Group I were even slightly better than in Group II. The conclusion seems to be inevitable that the lower fatality rate in Group II is due to the survival of patients with complications and sequelae.

Of the three patients of Group I with residual lesions, one was completely deaf at the time of discharge and showed no improvement three years later. Partial deafness existed in the second case; no improvement was noted three

years later. The third patient had a minimal amount of facial paralysis at the time of discharge; one year later complete recovery had taken place.

In Group II there were four patients who recovered from the infection but showed sequelae at the time of discharge. One of these patients had a marked foot-drop; six months later this condition had decidedly improved. The other three cases presented the picture of hydrocephalus associated with definite mental retardation.

That combined serum and sulfonamide therapy did not always result in sterilization of the spinal fluid within a few days, is evidenced by the observation that in eleven of sixty patients, the culture remained positive for more than five days after treatment was commenced. The survival of *H. influenzae*, however, does not imply by necessity an unfavorable prognosis; five of the eleven patients recovered, including one whose spinal fluid cultures remained positive for eleven days. In this connection, it is important to call attention to the fact that the spinal fluid of five patients became only temporarily sterile and that microorganisms reappeared at various periods after specific treatment was discontinued. It is imperative, therefore, to follow such cases with repeated spinal fluid examinations and, when indicated, to continue or resume specific therapy.

An attempt was made to appraise the specific therapeutic measures individually; namely, intravenous and intrathecal serum therapy, as well as treatment with sulfonamides. The interpretation of the data, however, is complicated by the fact that the series is not comprised of groups of patients who were treated with one therapeutic method exclusively. First considered is the problem whether or not a relationship exists between the total amount of serum administered intravenously and the case fatality rate. The data obtained are summarized in Table V, which reveals that five of eleven patients recovered with 100 mg. or less, and eight of twenty-six patients succumbed in spite of the administration of 200 mg. or more of antibody nitrogen. It is evident, therefore, that other factors, apart from the total amount of serum administered intravenously, determine the outcome of the disease.

TABLE V. RELATIONSHIP BETWEEN AMOUNT OF TYPE-SPECIFIC SERUM* ADMINISTERED INTRAVENOUSLY AND OUTCOME OF DISEASE

	UP TO 100		101 TO 200		201 TO 300		301 AND OVER	
Group I								
Recoveries	4	10	9	12	11	16	3	6
Fatalities	6		3		5		3	
Group II								
Recoveries	1	1	8	11	3	3	1	1
Fatalities	0		3		0		0	
Total								
Recoveries	5	11	17	23	14	19	4	7
Fatalities	6		6		5		3	

*Amount in milligrams of antibody nitrogen.

Although in the majority of recovered cases, sterilization of the cerebrospinal fluid was preceded by the presence of freely circulating antibodies in the blood, the presence of these antibodies in the blood did not always indicate

absence of viable microorganisms. This confirms observations reported previously (Neter[7]).

For the evaluation of intrathecal serum therapy (single dose of 25 mg. of antibody nitrogen) twenty patients were available. Naturally, it is not possible to compare these patients with those who received the serum only intravenously, since the former group includes patients who did not respond to intravenous serum therapy alone. The series of the intrathecally injected cases, however, throws some light on the beneficial and adverse effects resulting from this therapy.

In four cases serum was given intraspinally or intracisternally at a time when many microorganisms were still present in the cerebrospinal fluid. These patients succumbed to the infection. It is interesting to note that in three instances, the spinal fluid cultures remained positive for *H. influenzae* during the entire period of observation. That the infection per se was not controlled by this form of therapy is evidenced by the results of the post-mortem examination of three patients, which revealed the presence of diffuse exudative meningitis. It is evident, therefore, that serum administered intrathecally to patients whose spinal fluid contained a considerable amount of specific soluble substance and numerous bacilli, was ineffective and may have been even detrimental. An adverse effect of intrathecally injected serum could have resulted from the action of the antibodies with the antigen present in soluble form as well as in the capsules of the bacilli, causing the formation of precipitates and clumps within the central nervous system. In 1938, Finland, Brown, and Rauh[9] expressed the opinion that the administration of type-specific serum into the spinal canal in an otherwise untreated case of pneumococcal meningitis may result in harmful effects. Wheeler[10] suggested that similar conditions may prevail in meningitis due to *H. influenzae*.

Of sixteen patients, who were given type-specific serum at a time when but few microorganisms were present in the spinal fluid, thirteen recovered and three succumbed to the infection. The role played by the intrathecally injected serum is difficult to appraise because preceding treatment had produced a decrease in the number of viable organisms. However, from certain clinical and bacteriologic observations of these cases, the impression is gained that serum injected intrathecally at the proper time resulted in a favorable response in certain instances. For example, in two cases the temperature had been ranging between 101 and 104° F. Within twenty-four hours after the administration of 25 mg. of serum into the cisterna, the temperature dropped to normal and remained so until the time of discharge. In other cases the intrathecal injection was followed by a gradual improvement. No clinical response was noted in three patients.

From a bacteriologic point of view it is interesting to note that sterilization of the cerebrospinal fluid followed the intrathecal injection of type-specific serum in three cases. The recovery of these patients may be due, indeed, to the action of the locally applied antibodies. Regarding those patients who responded favorably from a clinical point of view and whose spinal fluid cultures were found to be sterile prior to this form of therapy, two explanations

for the clinical improvement present themselves. It is conceivable that viable microorganisms were present in the meninges, although none could be demonstrated by culture, and that the serum caused elimination of these bacilli. On the other hand, the favorable clinical course may be due to nonspecific effects of the serum.

The question whether intracisternal administration of serum is preferable to intraspinal injections may be answered on the basis of the following observations. Of a group of six patients who received the serum intraspinally, five recovered, and among ten patients who were treated intracisternally, nine made a recovery. Thus no appreciable difference was noted between the two methods of intrathecal serum administration.

It is generally agreed that in meningitis due to *H. influenzae*, sulfonamides should be employed as adjuncts to serum therapy. The sixty patients of this series received one or several of various sulfonamide compounds, namely, sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. Forty-eight cases lend themselves to analysis. Ten patients were treated with sulfathiazole. The resulting levels in the blood ranged from 5 to 8 mg. per cent. Of these patients, six recovered and four succumbed to the infection. Of the thirty-eight patients treated with sulfadiazine, twenty-nine recovered and nine died. The blood levels ranged between 10 and 25 mg. per cent. Although the difference in the case fatality rates is very slight, if at all statistically significant, it appears that sulfadiazine is preferable to sulfathiazole.

Regarding reactions to the anti-*H. influenzae* serum and the sulfonamides, the following observations have been made. In no instance was sensitivity to the serum so marked as to render its administration impossible. Immediate reactions to the serum, consisting of cyanosis, labored respiration, wheezing, cough, and urticaria, were encountered in seven instances. The reactions generally were mild and promptly relieved by adrenalin. Delayed serum reaction (urticaria-like rash) was encountered in eight instances. The intrathecal administration of serum caused reactions in three cases; namely, a generalized convulsive state in two and a sudden rise in temperature in the third patient. Fatal reactions were not encountered.

Complications other than cyanosis resulting from chemotherapy were observed in fourteen of the sixty patients. Hematuria occurred in thirteen instances; it was promptly controlled by reducing the amount of the drug, increasing the fluid intake, and alkalinizing the urine.

In only one instance was the influenza bacillus infection associated with a purulent lesion outside the central nervous system. This occurred in a 15-month-old white female who was comatose and in a moribund condition on admission. Multiple petechiae were noted. The patient was in shock, the blood pressure being 70/30 mm. Hg. Following the administration of type-specific serum, sulfadiazine, plasma, whole blood, and adrenal cortical extract, the patient gradually improved and recovered from the meningitis. However, on the fifteenth day of hospitalization the blood culture again became positive and the child developed purulent arthritis of the right knee joint. *H. influenzae* was recovered from the exudate. Following the intravenous adminis-

tration of 250 mg. of antibody nitrogen the patient recovered from this complication. At the time of discharge, hydrocephalus was present and the child was mentally retarded, as a sequela of the meningitis.

Two additional cases are included here because they illustrate that the classical picture of the so-called Waterhouse-Friderichsen syndrome or its initial stage, may be due to an infection with *H. influenzae*. These two patients are not included in the series itself, since they succumbed to the infection before it was possible to commence specific serum therapy. In one of these cases, post-mortem examination revealed the presence of massive diffuse hemorrhages of both adrenal glands. Meningitis, bacteriologically proved to be due to influenza bacillus type B, was also present. Interestingly enough, there were no petechiae. In the second case, post-mortem examination showed a superficial hemorrhage into the right adrenal gland; the left was normal. Had the child lived longer, more extensive hemorrhages might have developed.

DISCUSSION

The present series of sixty bacteriologically proved cases of meningitis due to *H. influenzae*, treated with type B specific antiserum and sulfonamides, illustrates the advances made in the treatment of this malady, as well as certain important failures. The effectiveness of these therapeutic agents has been definitely established and is reflected in this series by an uncorrected case fatality rate of 33⅓ per cent as compared with over 90 per cent in untreated cases. It is worthy of note that 19 of 35 patients under 2 years of age recovered. This recovery rate of approximately 54 per cent compares favorably with the recovery rate of 3 per cent of 152 cases not treated by specific measures. On the other hand, it is evident that in spite of all attempts to initiate specific treatment as soon as possible, to procure an adequate antibody titer in the patient's blood, and to maintain fairly high sulfonamide levels, one-third of these patients succumbed to the infection. Failure of therapy is particularly striking in young infants: only one of six patients less than 6 months old recovered from this illness. This age group presents the greatest challenge to therapy.

Another aspect of considerable importance in the cases presented here is the relatively high incidence of complications and sequelae. Seven of these sixty patients belong to this group. Aside from facial paralysis, partial or complete deafness, and foot drop, the most serious complication of the disease was marked hydrocephalus associated with mental retardation. It is not possible to state with any degree of certainty whether the development of hydrocephalus could have been prevented by a different management of therapy. It must be stressed that two of the three patients were given antiserum intrathecally at a time when but few microorganisms were present in the spinal fluid with a correspondingly low content of specific soluble substance. Whether or not this treatment contributed to the development of hydrocephalus, is a moot question that deserves further attention. It is felt that even with the experiences just mentioned, this form of treatment for well-selected cases should not be condemned at the present time. Clinically, several

patients responded favorably to the intrathecal administration of serum, and in several instances this form of therapy was followed by sterilization of the spinal fluid. The observations here reported seem to substantiate the opinion expressed by Finland, Brown, and Rauh,[9] as well as by Wheeler,[10] to the effect that serum injected intrathecally at a time when many organisms are present in the spinal fluid may have deleterious effects. Four such patients were observed all of whom succumbed to the infection. Of course, it is possible that the prognosis in these cases was poor, precisely because so many organisms were present. However, other patients whose spinal fluid contained equally as many microorganisms made an uneventful recovery.

From the reports in the literature and the experience with these sixty cases, the following conclusions may be drawn: (1) It is imperative that a diagnosis be made at the earliest possible time. (2) Treatment should consist of the administration (either intravenously or intramuscularly) of type-specific rabbit serum and sulfonamides, preferably sulfadiazine. (3) Adequacy of therapy should be established not only by the examination of the blood for free antibodies, but also by complete studies of the cerebrospinal fluid. Recrudescences should be recognized as soon as possible and dealt with accordingly. (4) Bacteriologic and clinical observations indicate that in certain selected patients intrathecal serum administration may be used with benefit to supplement intravenous serum therapy. Possible deleterious effects must be kept in mind and further investigations into this problem are definitely needed. Intrathecal injection of serum to patients whose spinal fluid contained many bacilli proved to be entirely ineffective and probably harmful. (5) Studies on the prevention of hydrocephalus as a complication or sequela of this malady are urgently needed. (6) The effectiveness of penicillin and other antibiotic therapy in this malady requires further investigation.

SUMMARY

Sixty cases of *H. influenzae* type B meningitis in infants and children treated with Alexander's type-specific rabbit serum and sulfonamides were analyzed. These cases were divided into two groups: Group I is comprised of all cases up to Oct. 1, 1944, and Group II from Oct. 1, 1944 to May 31, 1945. The following data were obtained:

1. Bacteriemia was present in thirty-nine of fifty cases (78 per cent).

2. The case fatality rate was 33⅓ per cent for the entire series, 38.7 per cent for Group I, and 18.7 per cent for Group II; for children under 2 years of age it amounted to 45.7 per cent.

3. Of the sixty patients, thirty-two had completely recovered at the time of discharge from the hospital. There was no appreciable difference in the rate of complete recoveries between the two groups.

4. The following complications and sequelae were encountered: purulent arthritis, facial paralysis, partial and complete deafness, foot drop, and hydrocephalus associated with mental retardation.

5. The total amount of intravenously injected serum was not the sole factor responsible for the outcome of the disease. Of particular significance is

the fact that eight of twenty-six patients succumbed in spite of the administration of more than 200 mg. of antibody nitrogen, including three of seven patients who received more than 300 mg.

6. All four patients who received serum intrathecally, at a time when many microorganisms and a correspondingly large amount of specific soluble substance were present in the spinal fluid, succumbed to the infection. The possible deleterious effects of this therapy have been discussed. Intrathecal injection of serum in patients whose spinal fluid contained but a small number of microorganisms or none at all was followed, in several instances, by clinical improvement and sterilization of the spinal fluid. The possibility that this form of therapy may have been responsible, in part at least, for the development of hydrocephalus in two patients has been considered.

7. Immediate reactions to the type-specific serum injected intravenously were encountered in seven instances; delayed reactions, in eight. Intrathecal injection of serum resulted in convulsions in two patients and fever in one.

8. Two cases, presenting, respectively, the initial stage and the classical picture of the Waterhouse-Friderichsen syndrome as seen on post-mortem examination, have been reported.

REFERENCES

1. Alexander, H. E.: J. PEDIAT. 25: 517, 1944.
2. Turner, E. K.: M. J. Australia 1: 219, 1945.
3. Comly, H. H., and McKee, A. P.: J. Iowa M. Soc. 35: 127, 1945.
4. Birdsong, M., Waddell, W. W., and Whitehead, B. W.: Am. J. Dis. Child. 67: 194, 1944.
5. Boisvert, P. L., Fousek, M. D., and Grossman, M. F.: J. A. M. A. 124: 220, 1944.
6. Scully, J. P., and Menten, M. L.: J. PEDIAT. 21: 198, 1942.
7. Neter, E.: J. PEDIAT. 20: 699, 1942.
8. Silverthorne, N.: Canad. M. A. J. 52: 252, 1945.
9. Finland, M., Brown, J. W., and Rauh, A. E.: New England J. Med. 218: 1033, 1938.
10. Wheeler, K.: Personal communication.
11. Smith, M. H. D., Wilson, P. E., and Hodes, H. L.: J. A. M. A. 130: 331, 1946.

AURICULAR FIBRILLATION IN INFANCY

Report of a Case With Fleeting Paroxysms

Joseph Edeiken, M.D., and Stanley J. Rugel, M.D.
Philadelphia, Pa.

In 1938 Goldbloom and Segall[1] reported a case of auricular fibrillation in an infant 3 months old and stated that an exhaustive search of the literature had not revealed a report of a single case of auricular fibrillation in the first year of life. We wish to report a second case first observed by us in 1943; to the best of our knowledge no other report has appeared in the literature since 1938. This case is of interest not only because of the rarity of auricular fibrillation in infants, but also because the irregularity was due to fleeting paroxysms of auricular fibrillation of the type described by several workers and discussed thoroughly by Wolferth in 1925.[2]

CASE REPORT

K. C., born April 12, 1943, was first seen by one of us when she was 2 months of age. The birth history revealed that she had been a blue baby. Except for a marked irregularity of the heart, physical examination was not significant. The heart action was very rapid and the arrhythmia of the totally irregular variety. No murmurs or cardiac enlargement could be made out at this time and there was no cyanosis present.

On July 9, 1943, when the baby was 3 months old, an electrocardiogram (Fig. 1) was made. This tracing showed paroxysms of auricular fibrillation with a rapid ventricular rate; the paroxysms were very short and followed a conducted beat. At this time, digitalization was begun, starting with a daily dose of ½ grain. Small dose therapy was continued for several months during which time no apparent effect on the arrhythmia or on the rapid ventricular rate could be detected. The rate, counted with some difficulty, varied between 140 and 200. When the child was 5 months old, for the first time a high-pitched, systolic murmur was heard in the second interspace to the left of the midline. A month later on Oct. 12, 1943, a second electrocardiogram showed little change over the first. There was still marked irregularity due to transient auricular fibrillation. At this time the murmur had increased in intensity and could be heard over the whole precordium. There was an associated systolic thrill present. An x-ray examination of the chest revealed the cardiac shadow to be of the "Dutch shoe" type and showed some enlargement.

Since the rapid cardiac rate showed little tendency to slowing and the baby's general condition seemed to be worse, it was decided to use larger doses of digitalis. For a period of several weeks a daily dose of 1½ grains was used and this appeared to keep the rate below 140 and the rhythm slightly more regular. Improvement continued until the middle of November when vomiting started, and in spite of discontinuing digitalis, persisted to such an extent that hospitalization was found necessary. On Nov. 20, 1943, the baby was admitted to the Jewish Hospital of Philadelphia on the pediatric service of Dr. Robert Schless. A few days after admission, quite suddenly, the baby died. Unfortunately a post-mortem examination could not be obtained.

DISCUSSION

Although a review of the literature indicates that auricular fibrillation is extremely rare in the newborn, irregularities, including auricular fibrillation have been described during fetal life. Hyman[3] secured phonocardiograms of three types of arrhythmias in the fetus-sinus arrhythmia, ventricular extrasystoles, and auricular fibrillation. Extrasystoles[4, 5, 6, 7] and auricular flutter[8, 9]

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, and the Jewish Hospital.

have been reported in infants, and instances of paroxysmal tachycardia[10] sometimes with extremely rapid ventricular rate have also been described.

In the case reported by Goldbloom and Segall,[1] auricular fibrillation was demonstrated at the age of 3 months in an infant whose heart was otherwise normal. Digitalis effectively reduced the ventricular rate and normal rhythm was restored spontaneously in the twelfth month and persisted to the date of publication. Our case differs in that the arrhythmia occurred in an infant with congenital heart disease and also because the paroxysms of fibrillation were

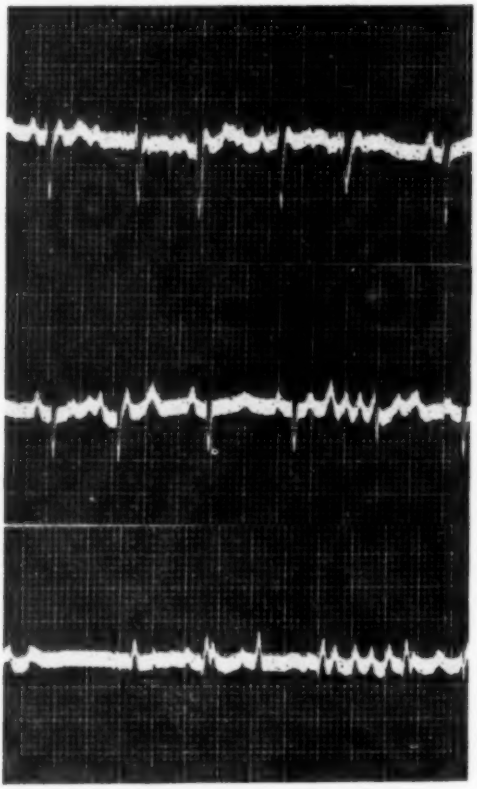


Fig. 1.

Although digitalis was effective in Goldbloom and Segall's case, no marked reduction in ventricular rate was noted in our case. In man auricular fibrillation and flutter are usually precipitated by auricular extrasystoles. Although circus rhythm occurs in auricular muscle which is in the stage of what Garrey[11] called the "fibrillary state" and such a state is most likely to exist at the time of extrasystoles, Garrey stated that auricular fibrillation may also be precipitated by a normal impulse from the sinus node. Garrey showed that "such fibrillary beats are initiated in the normal way from the normal pacemaker, that

the impulse shuttles back and forth through the auricular muscle producing rapid oscillations, which may stop before the next impulse arises so that the normal rhythm is not disturbed in the least." The paroxysms in our case appeared to be initiated by a normal impulse rather than extrasystoles. In 1918, Semerau[12] reported two cases of short paroxysms of auricular fibrillation which were thought to be precipitated by normal sinus impulses and, in 1940, Hecht and Johnston[13] reported a case of fleeting paroxysm of auricular flutter initiated by a normal sinus beat.

If auricular fibrillation occurs only when the auricular muscle is in the so-called "fibrillary state" one may speculate that the short paroxysm may be due to a temporary return to the normal state or to a derangement of the mechanism necessary to maintain fibrillation. Although very few cases of fleeting paroxysms of auricular fibrillation or flutter have been reported in the literature, this may be due to the difficulty of recognizing such brief paroxysms or they may be too brief to record. In 1925, Wolferth found only four cases reported in the literature with electrocardiograms that left no doubt as to the correctness of the interpretation and reported another case; in the same year Wolferth[14] reported two cases with fleeting paroxysms of auricular flutter.

Permanent fibrillation is rarely observed in normal hearts, but it is not unusual to observe paroxysmal fibrillation in adults whose hearts are otherwise normal. However, neither type had been reported in infants until 1938 when Goldbloom and Segall reported their case, attesting to the rarity of this condition in infancy and the possibility that when fibrillation does occur in infants it is usually too fleeting to be recognized or recorded. Garrey stated that the tendency to recover from fibrillation is in inverse ratio to the tissue mass, probably because greater mass and thickness of tissue afford the pathways for the development of the fibrillary circuits which sustain the fibrillary state.

SUMMARY

Auricular fibrillation of the fleeting type occurring in an infant with signs of congenital heart disease was followed from the age of 2 months to its fatal termination seven months later. Digitalis was only partially effective in controlling the ventricular rate. Auricular fibrillation in the newborn infant is rare, only one other instance having been reported in the literature. This case differed from ours in that the fibrillation was continuous and was controlled by digitalis.

REFERENCES

1. Goldbloom, A., and Segall, H. N.: Am. J. Dis. Child. 56: 587, 1938.
2. Wolferth, C. C.: Arch. Int. Med. 36: 735, 1925.
3. Hyman, A. S.: Am. J. Obst. & Gynec. 20: 332, 1930.
4. Lyon, R. A., and Rauh, L. W.: Am. J. Dis. Child. 57: 278, 1939.
5. Burghard, E., and Wunnerlich, A.: Ztschr. f. Kinderh. 45: 56, 1927.
6. Londe, S.: Am. J. Dis. Child. 44: 110, 1932.
7. Bass, M. H.: J. A. M. A. 86: 387, 1926.
8. Carr, J. G., and McClure, W. B.: Am. Heart J. 6: 824, 1931.
9. Willius, F. A., and Amberg, S.: Am. J. Dis. Child. 38: 551, 1929.
10. Edeiken, J.: Am. J. M. Sc. 205: 52, 1943.
11. Garrey, W. E.: Physiol. Rev. 4: 215, 1924.
12. Semerau, M.: Deutsches Arch. f. klin. Med. 126: 161, 1918.
13. Hecht, H., and Johnston, F. D.: Am. Heart J. 19: 237, 1940.
14. Wolferth, C. C.: Arch. Int. Med. 35: 42, 1925.

EXTREME PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Case Report

Nathan Bloom, M.D., and Edwin L. Kendig, Jr., M.D.
Richmond, Va.

PAROXYSMAL supraventricular tachycardia is a condition in which the heart beats rapidly and regularly in response to impulses arising in the auricles or above the bundle of His. The usual episodes are characterized by abrupt transitions from normal rhythm to tachycardia at their onset and from tachycardia to normal rhythm at their termination. These attacks seldom last over a few hours and at the most from five to six days. The heart rate is usually between 150 and 250 a minute; faster rates do occur but are rare because the ventricles are unable to respond to stimuli from the auricles over 300 a minute. Edeiken,[1] in a review of the literature, found that the upper limit at which the ventricles of the adult human heart can beat for a relatively prolonged period is about 300 a minute, although in infancy several cases with a higher rate have been recorded.

A study of our electrocardiographic files over the past ten years did not reveal any tachycardias at this faster rate and, as only seventeen cases have been recorded in the literature, we are presenting this additional report.

CASE REPORT

A 7½-month-old white infant was admitted to the Medical College Hospital on April 23, 1945. The child had been normal in every respect up to April 14, 1945, when he became fretful and restless and developed a slight cough and rectal temperature of 102° F. He was given antipyretic powders but continued to cough and had some difficulty in breathing, with no cyanosis. On April 20 he was given small doses of sulfadiazine. The morning of April 22 the infant's heart rate was 180 and, as he continued to be listless and the tachycardia persisted, the parents brought the child to the hospital on the night of April 23.

Examination.—The baby was well nourished and weighed 16 pounds, 13 ounces. The temperature was 101° F., respiration 40. There was no cyanosis. He was restless but took nourishment well without regurgitation. The neck veins were moderately distended and a few coarse ronchi were heard in the lung bases. The heart sounds were extremely rapid and trip hammer in quality. There were no murmurs. The apical rate was difficult to count but was well over 280 per minute. The liver edge was palpated two fingerbreadths below the right costal margin. There was no peripheral edema.

Laboratory Data.—The urine was acid, with 2 plus albumin, negative sugar, and a normal sediment. The red blood count was 3,610,000, with a hemoglobin of 73 per cent Sahli. The white blood count was 13,000, with 39 polymorphonuclear neutrophile leucocytes, 1 eosinophile, 58 lymphocytes, 1 normoblast, and 2 endothelial cells. The Wassermann was negative.

X-ray of the chest showed the transverse of the heart to be 9.4 cm., transverse of the thorax 15.2 cm.; the cardiothoracic ratio was 62 per cent. The left side of the heart was enlarged and there was a slight increase in the hilar lung markings.

From Departments of Medicine and Pediatrics, Medical College of Virginia.

The electrocardiogram on April 24, 1945, showed a supraventricular tachycardia, with a ventricular rate of 300 per minute. A second tracing after digitalization, on April 26, 1945, showed a regular rhythm, with a ventricular rate of 136.

Clinical Course.—While in the hospital, the infant was restless and fretful but continued to take nourishment. Carotid sinus pressure had no effect on the tachycardia. Intramuscular digitalis was started, in 0.25 cat unit dosages, and continued for twenty hours. During this time, 2.5 cat units were given; twenty-one hours after the last dose the heart rate returned to normal. No further medication was given, but after forty-eight hours the tachycardia recurred, lasting for several hours. The venous engorgement and liver enlargement disappeared after the rate slowed to 136 per minute.

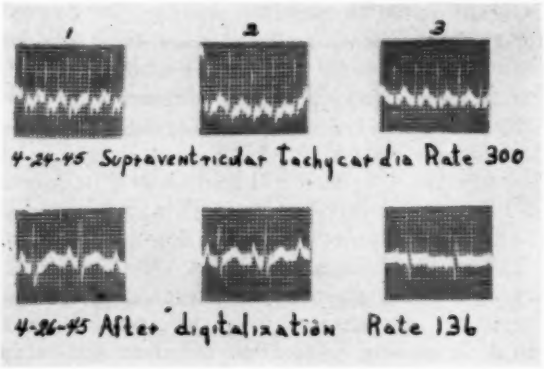


Fig. 1.—Extreme supraventricular tachycardia before and after digitalization.

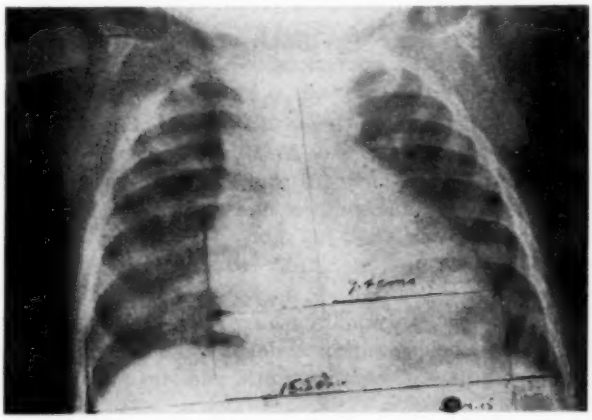


Fig. 2.—Roentgenogram of the chest showing diffuse cardiac enlargement, cardiothoracic ratio 62 per cent.

The child was discharged six days after admission but, after several days at home, the tachycardia returned. The child was then taken to Johns Hopkins Hospital and seen by Dr. Helen Taussig. At that time the digitalis was repeated and in a few days the tachycardia disappeared.

The infant has been continued on eight drops of tincture of digitalis since then and was seen by one of us (E. L. K.) on June 1, 1945. The child seemed perfectly normal and had gained a pound. The heart rate was 136 and an electrocardiogram was similar in every respect to our last tracing.

DISCUSSION

We believe that a distinction should be made between supraventricular tachycardia occurring in a damaged heart, tachycardia with the usual rates, and extreme tachycardia. The first type may be very dangerous, because a damaged heart is unable to withstand any excess strain. Therefore, an attempt should be made to halt the tachycardia immediately. The drugs of choice in an adult are quinidine, digitalis, mecholyl, or magnesium sulphate. Frequently, carotid sinus pressure, ocular pressure, or gagging, will terminate an attack, but if these procedures fail, one is justified in using quinidine, preferably by mouth. The dosage is usually 3 grains given three times daily. This may gradually be increased and at times 15 grains three times daily may be required to halt an attack. This drug is not without danger and fatalities have been reported from its use. Digitalis will frequently terminate an attack, but should be used in full therapeutic doses. Mecholyl is a powerful parasympathetic drug and must be given subcutaneously in adult dose of from 10 to 25 mg.; probably a 2 to 5 mg. dose would be adequate in a child. The ill effects of mecholyl may be abolished very quickly by intramuscular atropine, so it is always wise to have atropine ready for use when mecholyl is given. Magnesium sulphate has been successful in causing a cessation of supraventricular tachycardia. It is used in 1 Gm. doses intravenously in adults and much smaller doses intramuscularly might be advocated in children. If the heart has not been previously damaged, the usual supraventricular tachycardias will respond to this treatment very promptly, and there is seldom any need for continuing treatment, as these individuals have normal hearts which do not seem to be embarrassed by an episode of tachycardia.

Extreme tachycardias apparently lie in a different category. They have been discovered more often in children and have seldom been associated with organic cardiac disease. It is doubtful whether the parasympathetic nervous system functions in very young children and certainly we should hesitate in using toxic cardiac drugs on these infants. Digitalis is probably the least harmful of these drugs. Quinidine might be used orally in small doses, but we should hesitate to advocate either mecholyl or magnesium sulphate. It is our belief that if a physician would have courage enough to withhold medication for an attack, it probably would terminate without the use of any drug, as the ectopic focus would finally become fatigued and allow the sinoauricular node to take over its normal function.

The extreme tachycardia in this infant lasted four days and afterwards there were several recurrences. Although cardiac dilatation is an uncommon complication in paroxysmal tachycardia (Levine[2]), it did occur in our case. All of us who saw this infant were convinced that he did not have intrinsic cardiac disease, but it is quite possible that cardiac weakness might develop later, on account of the terrific strain on the myocardium.

Edeiken[1] concluded that drug therapy had very little effect on any of the previously reported cases and we must admit that in our case the tachycardia did not terminate until twenty-one hours after the last dose of digitalis. One might assume that there was a cumulative effect, but as the drug was given intramuscularly, it should have terminated the attack much earlier. We believe that there is very little indication for the continuance of digitalis in patients who have suffered attacks of tachycardia. It would seem better to use drugs during an attack, rather than attempt to prevent the attack.

SUMMARY

Extreme supraventricular tachycardia is probably not as rare as it would appear from the literature. Many cases are probably not discovered because of their sudden onset and spontaneous termination. The treatment of choice in infants is digitalis, but prognosis is good if there is no underlying cardiac disease.

REFERENCES

1. Edeiken, J.: Am. J. M. Sc. 205: 52, 1943.
2. Levine, S. A.: Clinical Heart Disease, Philadelphia, 1945, W. B. Saunders Company, p. 316.

CORONARY THROMBOSIS

Report of a Case in an Infant Eleven Months of Age

Edwin Paul Scott, M.D., and A. J. Miller, M.D.
Louisville, Ky.

A REVIEW of the literature reveals that coronary thrombosis in infancy is extremely rare. Coronary thrombosis has been reported by Hughes and Perry[1] (1929) in an infant 7 weeks of age and Ramsey and Crumrine[2] (1931) in an infant 4 months of age.

It is the purpose of this communication to record a case of coronary thrombosis in an infant 11 months of age.

CASE REPORT

History.—D. P., an 11-month-old male infant, was admitted to the Children's Free Hospital of Louisville, Ky., August 18, 1944, with the chief complaints of vomiting, cyanosis, and irritability. The child had been irritable for the past two weeks, especially at night, and had vomited and refused food for two days prior to admission. Intermittent cyanosis developed the day before admission.

Past history revealed that the delivery was normal; he had been admitted to the General Hospital, March 19, 1944, with diarrhea, otitis media, stiff neck, and a rash of two days' duration. Physical examination at that time revealed the following: dry lips, flaccid left leg, generalized erythematous rash, enlarged cervical nodes, reddened left tympanic membrane, and weight of 16 pounds.

Laboratory studies at that time showed the following: Roentgenograms of long bones, skull, and chest were negative; spinal fluid revealed sugar, 66.6 mg. per cent, protein 70 mg. per cent, chlorides 742 mg. per cent, and a cell count of 12 lymphocytes. Blood, stool, and throat cultures, tuberculin, Schick, Kahn, urinalysis, and agglutinations for typhoid, paratyphoid A and B were all negative. The white blood cells ranged from 12,250 to 8,750 cells per cubic millimeter and red cells from 4,060,000 to 3,590,000 per cubic millimeter with a hemoglobin of 10.5 Gm. per 100 c.c. of blood. The electroencephalogram was interpreted as abnormal for an infant because of the lack of any fast wave forms and low frequency high voltage delta waves in the occiput. There also was evidence that visual stimulation did influence the occipital wave form.

The infant remained in the hospital for a period of thirty-six days, lost weight, and ran a spiking type of temperature for three weeks. Treatment consisted of sulfathiazole, sulfadiazine, ear irrigations, buttermilk, vitamins, and transfusions of whole blood and plasma. Schilder's disease was considered, but he was discharged April 24, 1944, with a diagnosis of toxic encephalitis, nonspecific diarrhea, and left otitis media.

He was seen periodically in the Out-Patient Clinic up to May 29, 1944, at which time he had gained to 16 pounds. He was still unable to sit alone.

The family history revealed that the mother had several convulsions during the gestation period. There were six siblings living and well.

Physical Examination.—On admission to the hospital August 18, 1944, the physical examination revealed a well-developed and well-nourished white male, who was very restless and cyanotic. Respirations were rapid and breath sounds were exaggerated, but no râles could be heard. The heart rate was regular and no murmurs could be detected. The lower

From Department of Pediatrics, services of Drs. James W. Bruce and W. W. Nicholson and Department of Pathology, University of Louisville School of Medicine.

extremities were flaccid and the deep reflexes were sluggish to absent. There was marked weakness of the back and the infant was unable to sit alone. The temperature was 99.4° F. and the weight was 17 pounds, and 14 ounces. The clinical impression was bronchopneumonia.

Laboratory.—The initial white blood cell count was 24,600 per cubic millimeter with a differential of polymorphonuclear leucocytes 70 per cent and lymphocytes 30 per cent.

Course and Treatment.—The infant was immediately placed in a continuous oxygen tent and 10,000 units of penicillin were given intramuscularly. One and one-quarter hours following admission the child became cyanotic, started crying and gasping for breath. Despite all emergency measures the infant expired ten minutes later.

Post-Mortem Examination.—The pericardial cavity was entirely obliterated by dense fibrous adhesions. The heart was enlarged to three times normal size and weighed 130 grams. As the pericardium was dissected away from the epicardium there were large firm prominences noted in the region of the atrioventricular sulcus and these were found to be markedly enlarged coronary vessels. On cut section the vessels were enlarged to as much as one centimeter in diameter but having a lumen that barely admitted a fine probe. These changes involved the proximal portion of the right coronary artery and ended abruptly at a point where the vessel turned downward to become the posterior descending branch. The transverse branch and also the left marginal artery of the left coronary system were involved. Dissection of these vessels revealed them to be thrombosed with rather old blood which had undergone considerable organization.

Fig. 1.—Section of the left coronary artery.

The lungs were edematous and one and one-half times their normal weight and had many petechial hemorrhages on the pleural surfaces.

The liver weighed 240 grams and displayed marked venous congestion.

Unfortunately permission for head examination was not obtained.

Microscopy.—There was marked inflammatory reaction in both the pericardium and epicardium. Sections of the heart muscle revealed rather marked fibrosis and in one of the sections there was recent hemorrhage and necrosis which had the appearance of recent infarction. The coronary vessels were markedly enlarged because of dilatation and hyperplasia involving chiefly the intimal coat. In some sections all layers were hypertrophied with calcification at the periphery, in others there was necrosis of the media and adventitia, not unlike periarteritis nodosa. Many of the badly damaged vessels were occluded by inti-

nal thickening but had recanalized; in others the lumina were almost completely obliterated by thrombosis which had apparently been present for some time. The left coronary artery appeared to be completely occluded (Fig. 1*) resulting in an infarction seen in the myocardium.

The lungs revealed edema and vascular congestion and in some areas showed recent hemorrhage into the lung parenchyma.

The hilus lymph nodes contained caseous tubercles.

The pancreas revealed marked hyperplasia of one of the medium-sized arteries, but thorough examination of all other tissues failed to reveal any similar lesions.

COMMENT

Death in this child was due to coronary thrombosis. The lesions found in the coronary vessels and in one vessel of the pancreas were not unlike periarteritis nodosa but the changes in the vessel walls and the thrombosis were more suggestive of thromboarteritis obliterans.

CONCLUSION

Coronary thrombosis in an 11-month-old infant, with post-mortem findings, is herein reported.

REFERENCES

1. Hughes, F. W. T., and Perry, C. B.: Bristol Med. Chir. J. 46: 219, 1929.
2. Ramsey, R. E., and Crumrine, R. M.: Am. J. Dis. Child. 42: 107, 1931.

*Photography by Mr. W. L. Williams.

PNEUMOCOCCIC STOMATITIS

CAPTAIN CARL J. OCHS, MEDICAL CORPS
MIAMI, FLA.

THAT THE pneumococcus appears growing in the pharynx is a fact recorded by the textbooks. Pneumococci growing primarily in the mouth is not generally recognized, or, if the condition is observed, the cases have not appeared in the literature. Crawford[1] recorded nine cases which he had observed. These were the only cases it was possible to find recorded in the literature during the past twenty years. Textbooks on pediatrics, and on diseases of the mouth do not apparently recognize the condition, although Griffith and Mitchell[2] state that a pseudomembrane may be produced in the mouth by the pneumococcus, perhaps in the course of pneumonia. It is possible that cases of pneumococcic stomatitis may be appearing unrecognized. If the condition is as unusual as is indicated by the textbooks and the literature, the report of this case seems indicated.

A male infant, 5 weeks of age, was first seen in the Out-Patient Department of the Army Air Forces Regional and Convalescent Hospital at Coral Gables, Fla., Jan. 16, 1945. The mother stated that the child had been well until Jan. 2, 1945, when she first noticed that he began to be irritable and to refuse his formula. It was at this time that she observed white patches in his mouth which she assumed to be particles of milk. The patient was seen by a local physician who applied gentian violet to the mouth. The mouth appeared to clear and the child seemed well within a few days. On Jan. 9, 1945, the mother again noticed white patches in the mouth, but in spite of repeated applications of the gentian violet the mouth became gradually worse. At the time of his first visit the baby appeared to be normal in every way excepting for the lesions in the mouth.

The lesions were located on the buccal mucous membranes, on the gums, both above and below, on the tongue margin, and beneath the tongue. The membrane was thin, translucent, and was firmly adherent. The mucous membranes bled freely when the membrane was removed. There was no induration of the surrounding mucous membrane. There was no detectable odor. A smear made for Vincent's organisms was negative. It was assumed that this was probably a severe stomatitis due to thrush, and the mother was directed to intensify the gentian violet treatments and to return to the clinic in two days.

The baby was seen again Jan. 18, 1945. The mouth infection had become worse and the child was very irritable. He was admitted to the Jackson Memorial Hospital, military dependents' service. Penicillin, 250 units to the cubic centimeter, was applied locally every two hours in additon to the gentian violet. The following day, Jan. 19, 1945, the baby appeared to be worse. There was a quantity of mucus in the pharynx and he was coughing. It was feared that he might be developing a pneumonia although the chest remained clear. A smear of the membrane taken from the mouth failed to demonstrate any organisms. There were numerous, large squamous epithelial cells, and an occasional pus cell. The blood count taken at that time showed red blood cells 3.2; hemoglobin, 10.8 Gm., white blood cells, 7,950. The differential: stabs 2, segmented cells 16, total neutrophiles 21, lymphocytes 74, monocytes 3, eosinophiles 2. Penicillin therapy was begun; 3,000 units per cubic centimeter were given intramuscularly every three hours. The patient appeared to be critically ill and for that reason sulfadiazine, grains 1 per pound daily, was also given.

On January 20, there was no improvement. The breathing was more labored. The membrane in the mouth showed no change. X-ray of the chest showed no pathology to be present. The urine was normal. The culture taken from the membrane in the mouth January 18 was reported type XIV pneumococcus.

On January 21, the patient was apparently having tracheobronchitis, so that oxygen was administered. Atropine was given in an attempt to reduce the amount of secretion from the mouth. The membrane in the mouth persisted unchanged..

On January 22, the second culture from the membrane in the mouth was reported as type XIV pneumococcus, this time with a staphylococcic contaminant. The blood count showed red blood cells 3.3, hemoglobin 10.8 Gm., white blood cells 12,700. Differential: neutrophiles 61, lymphocytes 35, monocytes 2, and eosinophiles 2.

There was a definite difference in the appearance of the membrane in the mouth on January 24. The membrane, which had formerly been thin, now became thicker. It was beginning to free itself from the margins and was friable. The general appearance of the patient was much improved. The respirations were no longer labored and he began to take his formula.

On January 27, the membrane had cleared from the mouth and medication was discontinued. He had received a total of 165,000 units of penicillin intramuscularly. He was discharged from the hospital Feb. 3, 1945, apparently recovered.

Smears and cultures were taken from the nasopharynges of the mother and two grandmothers, the only people who had contact with the patient. These were reported negative for pneumococci.

The temperature of the patient at no time exceeded 101° F. A membrane was never observed in the pharynx.

REFERENCES

1. Crawford, J. A.: Tri-State M. J. 11: 2308, 1939.
2. Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 2, Philadelphia, 1937. W. B. Saunders Company, Vol. 2, p. 19.

RIGHT-SIDED TRANSIENT PARALYSIS OF THE DIAPHRAGM IN A NEWBORN INFANT

Case Report

J. Victor Greenebaum, M.D., and Forest G. Harper, M.D.
Cincinnati, Ohio

THE occurrence in the New Born Service at the Jewish Hospital of the first recognized case of isolated phrenic nerve injury with paralysis of the diaphragm merits a report since it is the eighth such recorded case. Paralysis of the diaphragm associated with brachial paralysis in newborn infants is likewise a rare condition—approximately twenty-five cases having been recorded to date. Zeligs,[1] in 1928, described the first case seen in Cincinnati. Diaphragmatic paralysis has been recognized since 1902, when Naunyn[2] reported the first case. Since then others[3] have reported occasional cases, but Kofferath[4] was the first to study an infant with paralysis of the diaphragm by means of the fluoroscope. He described the paradoxical movement of the affected diaphragm and showed that it was necessary to use fluoroscopy to rule out other pathologic conditions, which might be confusing if only a flat plate of the chest were taken and elevation of the diaphragm found. Their chief conditions to be differentiated are; intracranial hemorrhage, empyema, atelectasis, diaphragmatic hernia, and pneumonia. Congenital heart disease is also ruled out as to the cause of cyanosis and respiratory difficulty by the fact that fluoroscopic examination shows normal cardiac configuration and pulsations. Blattner,[5] in reviewing the six cases of unilateral diaphragmatic paralysis without brachial palsy reported previous to his, found that in four the diaphragm was paralyzed on the right side; whereas, it was paralyzed on the left side in the other two cases. In his own case, the right side of the diaphragm was paralyzed. His report is the most completely worked-up case—the only one with microscopic pathologic findings on the phrenic nerves. Degeneration of the phrenic nerve and of the muscle fibers of the diaphragm were the principal pathologic findings. Following the idea of Rupilius[6] Blattner believes that prenatal compression of the phrenic nerve due to the position of the fetus in utero during the last months of pregnancy, rather than obstetric manipulation, is the cause of this condition. He also stresses the importance of fluoroscopic examination in all newborn infants showing respiratory distress. The diagnosis was made of his patient at the age of 4 months. In the other six cases reviewed by him none of the patients showed symptoms at birth, the earliest symptoms appearing the third day. In our case symptoms began on the fourth day and fluoroscopic examination made on the seventh day disclosed a right-sided diaphragmatic paralysis.

CASE REPORT*

R. L. T. (Case No. 44-7739), a male infant, was born at the Jewish Hospital on Oct. 29, 1944, at 12:35 A.M., of a tall slender primipara with a small pelvis. The labor was

From the New Born Service and Roentgen Ray Department of the Jewish Hospital.
*Kindness of Dr. Frank J. Albers.

within normal limits, lasting eight hours. Pitocin was given at 12:06 A.M. and low forceps with good application to the head in a L. O. A. position were used with the patient under gas, oxygen, and ether anesthesia which was given for twenty-five minutes.

The infant was resuscitated with some difficulty, but after oxygen was given and a large amount of mucus was aspirated from the throat the baby cried well and was sent to the nursery in good condition. He weighed 9 pounds, 14 ounces. The baby did well for the first three days, nothing unusual being noticed by the nurses or physicians. He nursed at the breast and took the bottle containing complementary feedings well. On the fourth day (Nov. 1, 1944) it was noticed that the baby had some difficulty with his breathing and did not take his feedings well. Tentative diagnoses of intracranial hemorrhage or congenital heart disease were made due to the appearance of cyanosis on Nov. 3, 1944. One of us (J. V. G.) was requested to see the baby on Nov. 4, 1944, the seventh day of life. The infant vomited that day for the only time during his entire stay in the nursery.

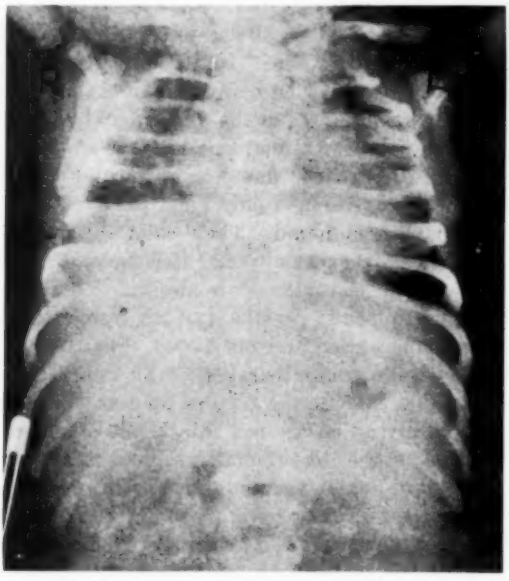


Fig. 1.—Roentgenogram (Nov. 4, 1944) showing elevation of right diaphragm.

Examination revealed a somewhat cyanotic, but well-developed and well-nourished, full-term, male infant lying on his back and breathing with difficulty. However, he cried well and resisted examination. The head had a caput succedaneum in the right occipital region. The pulse was 150 and the respirations were about 70 per minute. All extremities were normal. No paralysis was present. The fontaneles were level and of normal tension. The eyes, ears, throat, neck, abdomen, genitals, and the skin, except for cyanosis, were negative. The chief abnormal signs were in the chest. The respirations were rapid, thoracic in type and labored. The left chest moved in an exaggerated manner in contrast to the right side, which was relatively quiet. There was normal resonance throughout the left side with normal breath sounds. The right side showed impaired resonance throughout the back with diminished to absent breath sounds. The heart was rapid and a systolic murmur was present at the apex. There was no elevation of temperature at any time. A tentative diagnosis of atelectasis on the right side was made. A roentgenogram was ordered and a fluoroscopic examination was made at once. The fluoroscopic examination showed that the

baby was breathing only with the left side of the chest—the right side being practically immobile. At each respiration the mediastinum moved in a to-and-fro direction as a result of the paradoxical or see-saw movement of the diaphragm—the left side going down with inspiration while the right side, although appearing to be relatively fixed, raised a little during inspiration. The heart was displaced to the left and downward by the mediastinal shift, but the contour was normal. The roentgenogram (Fig. 1) confirmed the high diaphragm at the level of the fifth rib on the right side. In fact, there was a heated discussion, when this case report was made before the Staff Conference, particularly about the diagnosis of the roentgenogram. Several opinions were expressed that the diagnosis was simply atelectasis with the negative pressure in the right chest producing a high position of the diaphragm. As already stated, the diagnosis of diaphragmatic paralysis can only be suspected as one of several possibilities by a study of the flat plate of the chest; the final differentiation must be made by observing the infant under the fluoroscope. The diagnosis of paralysis of the right diaphragm was made and treatment was instituted at once.

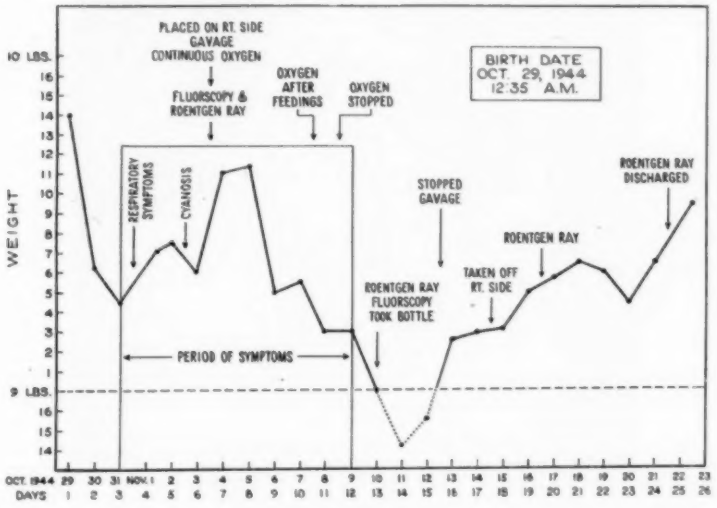


Fig. 2.—Weight chart and pertinent clinical data.

Treatment.—The infant was placed on the right side to splint it, oxygen was started continuously and gavage feedings were given. The cyanosis and respiratory distress were relieved to a surprising extent. The breathing became quiet and the heart rate decreased. The systolic murmur and the dullness of the right chest disappeared, while the breath sounds were heard equally throughout both lungs. However, the infant's respiration became embarrassed whenever he was taken off of his right side. Although there was some loss of weight for a few days, steady improvement began (weight chart Fig. 2). The stools were normal at all times and in two days the baby began to take the bottle again. Continuous oxygen was stopped and was administered only after feedings; it was discontinued entirely on Nov. 9, 1944—nine days after onset of symptoms.

A second roentgen ray and fluoroscopic examination on Nov. 11, 1944, showed definite increase in the movement of the right diaphragm and better aeration of the right lung. It was possible to place the baby on the back and left side for an increasing lengh of time on Nov. 14, 1944, without respiratory distress.

A third roentgen ray examination on Nov. 16, 1944 (Fig. 3), showed the condition to be practically normal and the baby was discharged in good condition on the twenty-sixth day (Nov. 26, 1944). The baby weighed 9½ pounds when discharged; this

was four ounces under the birth weight of 9 pounds, 14 ounces. After discharge to the home, he began immediately to show a normal weight gain. He has continued to do well and has been seen on Nov. 29, 1944, Jan. 12, 1945, Mar. 20, 1945, and on April 16, 1945, at which time fluoroscopic and roentgen ray examination showed a normally functioning diaphragm with no mediastinal shift and the heart in normal position. The baby was in excellent condition and breathed normally. When last seen at the age of 5 months, he weighed 15 pounds, 4 ounces.

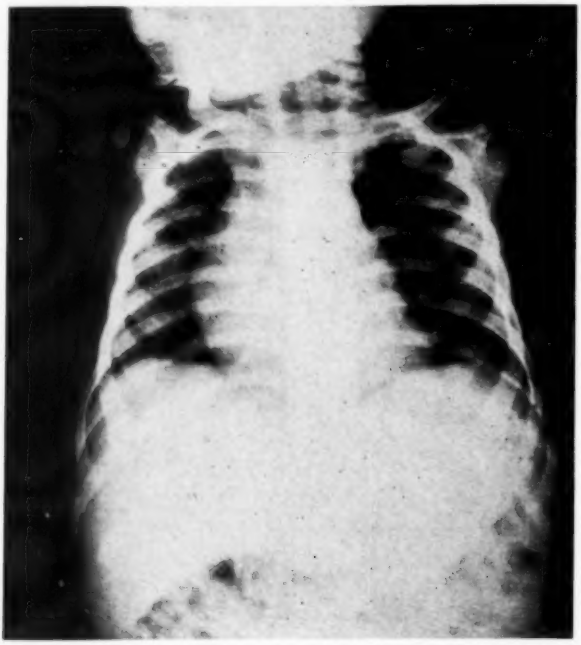


Fig. 3.—Roentgenogram (Nov. 16, 1944) showing normal position of right diaphragm. Baby's body rotated producing distorted position of heart.

DISCUSSION

In discussing this case and phrenic nerve paralysis of newborn infants in general, we wish to emphasize the following points: Although the condition is rare as far as reported cases are concerned, it can be justifiably deduced, as expressed by Friedman and Chamberlain,[7] that "Phrenic nerve injury in the new born cannot be so unusual an occurrence when we take into account the intimate relationship of this nerve to the brachial plexus. It is a reasonable assumption that any serious injury to the upper cord of this plexus is likely to involve in some measure the filaments that make up the phrenic nerve." It also seems reasonable to assume that the phrenic nerve can be injured without involvement of the brachial plexus. Kofferath, likewise expresses the belief that this type of injury is not very rare, especially when associated with Erb's palsy. It is almost invariably overlooked probably because cyanosis, the most prominent symptom it gives rise to, is common to numerous pathologic conditions frequently encountered in newborn infants.

It is suggested that phrenic nerve paralysis should be excluded in every case of brachial palsy. Furthermore, one should not fail to consider this condition in the differential diagnosis when the newborn baby displays cyanosis, irregular, labored, or accelerated breathing, unilateral diminution of breath sounds with or without moisture, or unaccountable gastric disturbances. When there is doubt, the infant should be fluoroscoped, for, when the possibility of the occurrence of diaphragmatic paralysis is once appreciated, its discovery is usually accomplished with ease.

SUMMARY

A case of transient paralysis of the right side of the diaphragm due to so-called isolated phrenic nerve injury in a newborn infant is reported. Signs of respiratory distress and cyanosis appeared on the fourth day of life. The diagnosis was made on the seventh day by means of fluoroscopy.

The relatively prompt relief of the symptoms with restoration of the function of the diaphragm nine days after symptoms began, and six days after institution of treatment, showed the transient nature of the phrenic nerve injury in this case. Regeneration of the injured nerve sufficient to allow normal impulses to the diaphragm was undoubtedly made possible by resting of the nerve through the method of treatment used which consisted of placing the infant on the right side to splint it and by giving continuous oxygen and gavage feedings. This case has the shortest duration on record of acute symptoms and signs commonly associated with diaphragmatic paralysis, and is the first one in which the described methods of treatment are reported.

This is the first recognized case of diaphragmatic paralysis in the New Born Service of the Jewish Hospital and is the eighth recorded case without accompanying brachial paralysis.

It is a pleasure to express our appreciation to Miss Billie Ann Craven, supervisor, of the New Born Service, and her corps of nurses and nurses' aides, for their intense interest in this unusual case. The constant care of this splendid group of women was, in our opinion, the largest factor in the rapid improvement and final recovery of this infant.

REFERENCES

1. Zeligs, M.: J. A. M. A. **90**: 762, 1928.
2. Naunyn, B.: Deutsche med. Wchnschr. **7**: 13, 1902.
3. Epstein, J. W.: Am. J. Dis. Child. **34**: 634, 1927.
   Stein, J. L.: J. PEDIAT. **3**: 471, 1933.
   Weigert, R.: Beitr. z. Klin. Chir. **119**: 100, 1920.
   Landsberger: Klin. Wchnschr. **5**: 850, 1926.
   Schweizer, F.: Semana méd. **34**: 1098, 1927.
   Sebolovitch, R.: Jahrb. f. Kinderh. **147**: 86, 1936.
   Kottgen, Hans-Ulrich: Arch. f. Kinderh. **113**: 165, 1938.
   Mulzer, A.: München. med. Wchnschr. **75**: 1498, 1928.
   Dyson, J. E.: J. A. M. A. **88**: 94, 1927.
   Remé, G.: Arch. f. Kindhr. **92**: 62, 1930.
   Tyson, R. M., and Bowman, J. E.: Am. J. Dis. Child. **46**: 30, 1933.
4. Kofferath, W.: Monatschr. f. Geburtsh. u. Gynäk **55**: 33, 1921.
5. Blattner, R. J.: J. PEDIAT. **20**: 223, 1942.
6. Rupilius, K.: Arch. f. Orthop. u. Unfall-Chir. **34**: 628, 1934.
7. Friedman, E., and Chamberlain, R. S.: J. A. M. A. **86**: 934, 1926.

LEPTOMENINGEAL CYST ASSOCIATED WITH HEMIPLEGIA AND SKULL DEFECT OF TRAUMATIC ORIGIN

MOSES COOPERSTOCK, M.D.
MARQUETTE, MICH.

AMONG the variable complications that follow severe craniocerebral trauma, the development of the syndrome of leptomeningeal cyst, hemiplegia, and skull defect is of relatively infrequent occurrence. Apparently, because of the striking roentgenologic features present, this condition has more sharply excited the attention and interest of roentgenologists. Dyke,[1] for example, not only presented a clear description of the roentgenologic changes, but also offered an explanation of the manner in which these changes take place. Since this condition occurs as frequently in children as in adults, the pediatrician, as a member of a clinical team, may find himself in a position of usefulness relating to the factors of diagnosis and decisions arising as to proper therapeutic management.

Leptomeningeal cysts are produced by severe head trauma invariably accompanied by skull fracture usually of the comminuted or depressed variety. They develop as the result of laceration of the arachnoid, pia mater, and, in many cases, the dura mater as well. Dyke believes that while hemorrhage may play an important role in the formation of these cysts, actually the areas of the subarachnoid space become separated from the general subarachnoid space in the process of healing of the lacerated membrane, forming cystic collections of fluid. The skull defect develops as a result of resorption of bone overlying the cyst and is brought about by the pulsating pressure of the brain, much in the same way in which bone resorption is produced by aortic aneurysms in their proximity to such bony structures as the sternum, ribs, and vertebrae. The neurologic changes result from destruction of the regional cortical tissue of the brain.

The following case report covers a ten-year period of observation of a patient from the time of her head injury to that of operation, thereby offering an unusual opportunity for study of the clinical aspects of this condition over a long period of time.

REPORT OF CASE

J. J., a 5-month-old girl infant, was admitted to the hospital on Aug. 1, 1933, five hours after an accident in which an aunt had fallen down a flight of stairs while carrying the baby. The patient was born at term, weighing 8½ pounds. She had been progressing satisfactorily, although it was thought that she was rather pale previous to her accident. Drowsiness, vomiting, and pallor were noted in the infant soon after the accident. Initial examination when the child was brought to the hospital revealed a blanched, semi-comatose infant, irritable when aroused. There was asymmetry of the skull produced by a soft swelling on the right side of the head extending from the anterior parietal area to the occiput. The skull underneath the swelling could not be satisfactorily palpated. There was

From the Northern Michigan Children's Clinic.

no evidence of bleeding from the various external orifices. No evidence of paralysis was made out at this time. No cranial nerve palsies or pathologic reflexes were detected. The hemoglobin was 60 per cent and the red blood count, 3,100,000. Roentgen examination confirmed the admission impression of skull fracture involving the right parietal bone.

The patient was treated conservatively with magnesium sulfate rectally and hypertonic glucose solution intravenously. Within twenty-four hours, the patient recovered from the initial shock symptoms and was able to nurse at the breast. She continued to improve rapidly thereafter and was discharged on the eighth hospital day. The day before her discharge, her hemoglobin was 65 per cent and her red blood count, 3,450,000.

Subsequent Course.—One week following discharge from the hospital, the swelling on the right side of the head had become considerably reduced in size. Aspiration of the mass yielded 15 c.c. of thin, hemorrhagic fluid. The hemoglobin had risen to 70 per cent and the red blood count to 3,820,000.

The patient was seen at frequent intervals over the next two years (1933 and 1934). The fluctuant mass over the right parietal area gradually decreased in size during this time. Definite increase in the tension of the mass could be made out when the patient cried, indicating the presence of its communication with the ventricular system. At the age of 7 months, weakness of the left arm was detected and at 11 months, weakness of the left leg with slight spasticity of both the left arm and leg became apparent. There was no associated facial paralysis. She learned to walk at 15 months. Her gait appeared to be hemiplegic in type. Spasticity of the left arm and leg became more marked and the gait more characteristically hemiplegic during the following two years (1935 and 1936). During this time, physiotherapeutic treatment was carried out. The swelling over the right parietal area had disappeared, revealing a large, palpable bony defect in the skull. With the ensuing years, moderate atrophy of the left arm and leg developed, the atrophy of the left arm being more pronounced than that of the leg. The shortening of the leg was sufficient to produce a limp of moderate degree together with a compensating curvature of the spine. There was no impairment of intelligence; in fact, she was an honor student in school.

In 1941, the question of operation presented itself when the diagnosis of leptomeningeal cyst was entertained. Because of the excellent mental status of the child and the doubt at the time as to the ultimate benefit offered by surgery, the matter of surgery was left in abeyance. The question of surgery was again considered two years later from the point of view of closing the skull defect with tantalum, in addition to the possible beneficial results to be obtained by removing any existing cystic structure. This course was decided upon and operation was performed (Jan. 24, 1944) by Dr. Max Peet, Head of the Department of Neurosurgery of the University Hospital, Ann Arbor, Mich., with whom the problem was discussed.

Summary of Operative Findings.—When the skin flap overlying the skull defect was reflected and dissected free, the defect was found to extend from the midline down toward the right ear for a distance of approximately 11 cm., measuring 5 cm. in width. The edges of the skull defect which were depressed were removed with the aid of the rongeur. A leptomeningeal cystic structure was opened and approximately 10 c.c. of fluid were removed. The cystic mass seemed to be made up of several cysts measuring from 0.5 cm. to 0.7 cm. The cortex of the underlying brain appeared to be destroyed for a depth of 2.0 cm. Scar tissue present in this area was removed, in the process of which a piece of detached bone was found and extracted. Another bone fragment was found inside of the longitudinal sinus. This was also removed. The bony defect was closed with a tantalum plate.

Summary of the Roentgenologic Findings.—Studies of the skull on the day of admission to the hospital (August 1, 1933) showed the presence of a fracture extending from the sagittal suture into the mid-portion of the right parietal bone (Fig. 1.). Also present in this area were less prominent linear fractures. There was a suggestion of the presence of a transverse fracture through the occipital squama. The presence of a depressed fracture in this film was not definitely apparent.

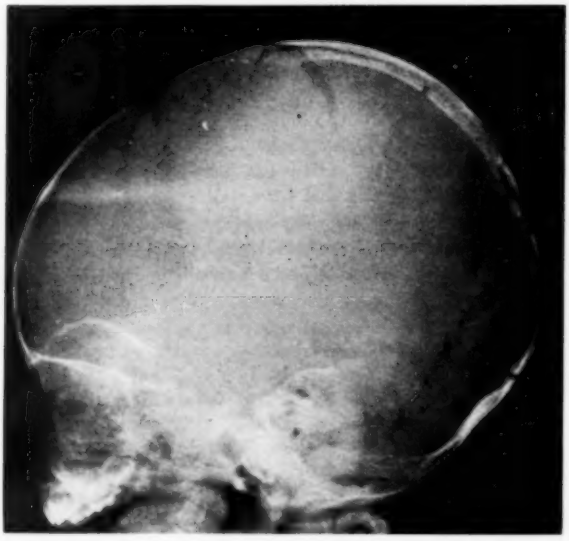


Fig. 1.—Admission roentgenogram (Aug. 1, 1933) showing a fracture extending from the sagittal suture into the mid-portion of the right parietal bone.

Fig. 2.—Illustrating the development of a large area of bone resorption in the area of the skull fracture four and one-half months after the accident (Dec. 15, 1933), made up of circumscribed areas of rarefaction with sclerotic changes at their margins, a scalloping effect produced in the inner table of the skull by the pressure of the leptomeningeal cyst.

By four and one-half months (Dec. 15, 1933), a large area of bone resorption had appeared roentgenologically, made up of circumscribed areas of rarefaction with slight sclerotic changes at their margins (Fig. 2.) corresponding to the scalloping effect of the inner table of the skull described by Dyke, produced by the presence of underlying cystic structure.

Roentgenograms of the skull obtained periodically over the ensuing years showed persistent failure of closure of the defect. There was suggestion of a disturbance of ossification as evidenced by the irregularly increased thickening of the skull in the involved area (Fig. 3.).

Fig. 3.—Roentgenogram taken eight years after the accident (Aug. 9, 1939) showing more striking development of the skull defect, the roentgenologic picture being practically the same at the time of operation, eighteen months later.

COMMENT

The special points of interest in this case, in addition to the recording of an unusual complication of craniocerebral injury, center around the importance of early diagnosis and treatment. Although the development of bone resorption in the area of an earlier, severe skull fracture together with the presence of hemiplegia appears clearly to indicate the formation of a leptomeningeal cyst, a valuable loss of time from the point of view of treatment would seem to be involved if one were to wait for the appearance of bony defect to complete the entire triad. Evidence of a depressed fracture, which commonly accompanies this condition, would doubtless by itself lead to early operative treatment. However, as in the patient here reported, in the absence of definite evidence of a depressed fracture, surgical treatment might be readily overlooked in favor of conservative management. The presence of hemiplegia together with evidence of skull fracture should point to a type of severe craniocerebral injury favorable to the production of a leptomeningeal cyst and thereby call for early surgical inter-

vention. In the case of the patient described here, hemiplegia was not detected at the time of injury; weakness of the arm was detected at two months and that of the leg six months later.* An awareness of its possible presence together with repeated roentgen examinations of the skull for the detection of the skull changes of bone resorption in such cases in young infants will doubtless lead to earlier diagnosis of leptomeningeal cystic formation and to early surgical treatment. Apparently, roentgenologic evidence of bone resorption takes place fairly early. In the patient reported here, such roentgenologic evidence was already well marked four and one-half months after the occurrence of the head injury. Unfortunately, earlier roentgenologic studies following the accident were not performed.

It is probable that an appreciable proportion of such cases occurring in infancy and childhood have gone on to adult life without realization of the true significance of the underlying pathology. Early operative intervention in similar craniocerebral injuries would seem important not only from the point of view of anticipating the development of skull defects, but also with the hope of minimizing the neurologic complications, particularly in patients belonging to the period of rapid growth. It is apparent that had the full significance of the underlying process been recognized earlier and surgical treatment instituted at that time, the patient reported here would have profited in a greater measure.

SUMMARY

An instance is recorded of the development of a leptomeningeal cyst, hemiplegia, and a persistent, large skull defect in a patient who had sustained a severe skull fracture at the age of 5 months and who was observed over a period of ten years.

The skull defect, appearing as a striking feature in this case, made its roentgenologic appearance within a period of several months and was the result of the presence of the underlying leptomeningeal cyst.

Some of the problems of diagnosis and the institution of proper treatment are discussed in the light of the observations in this case.

I am indebted to Dr. Vincent C. Johnson, formerly of the Department of Roentgenology, University of Michigan Hospital, Ann Arbor, Mich., for his interpretation of the roentgenograms.

REFERENCE

1. Dyke, C. G.: The Roentgen-Ray Diagnosis of Diseases of the Skull and Intracranial Contests in Diagnostic Roentgenology, Golden, Ross, editor, New York, 1941, Thomas Nelson & Sons.

*In his study of the evolution of hemiplegias, Byers (Byers, K. H.: Am. J. Dis. Child. 61: 915, 1941) notes that weakness and hypotonia may precede spasticity by months, thus obscuring the diagnosis of hemiplegia for considerable lengths of time.

BISMUTH NEPHROSIS WITH ANURIA IN AN INFANT

Report of a Case

Dan P. Boyette, M.D.
Ahoskie, N. C.

REPORTS of the toxic effects of bismuth are not new; many deaths have occurred following its use. The majority of these have occurred in adults who have received repeated doses of the metal or who had received it by accidental intravascular injection. Anuria as a symptom of bismuth toxicity has been reported,[1, 2] but death due to complete failure of kidney function is uncommon enough to merit mention.

Bismuth, one of the heavy metals, has been used medically for many years, but only recently have the toxic effects been studied.[1, 3, 4] In general, its pharmacologic action is similar to that of mercury, but the untoward reactions are far less frequent and are usually of a less serious nature. The toxic effects more commonly noted are stomatitis, gastroenteritis, nephrosis, and involvement of the central nervous system. The age and sex of the patient and the form of bismuth administered make no difference in degree of toxicity. The solubility of the preparation is the most influential factor, the more rapidly absorbed ones causing the greater protoplasmic destruction. Oil suspensions are least dangerous, and rapidly absorbable water solutions are most dangerous. Most bismuth compounds, when administered by mouth are not absorbed sufficiently from the gastrointestinal tract to allow the metal to reach any effective level in the blood and tissues.[3]

It has been shown that bismuth, since it is excreted mainly in the urine, is more toxic to the kidney than to any other organ.[5] The first effect is that of stimulation, resulting in diuresis, without renal damage being demonstrable. This may be followed by oliguria, then albuminuria, and finally, true nephrosis, at which stage edema and necrosis of the proximal tubules of the kidney can be recognized pathologically.

Complete anuria in an infant as the result of a single injection of a bismuth preparation in the treatment of Vincent's gingivostomatitis is rare. It is felt advisable to warn of the hazards of using such a drug by reporting a case that terminated fatally.

CASE REPORT

R. B., a 2-year-old, 20-pound, female infant, was admitted to the hospital on March 19, 1945, with the history of a "sore mouth" for six days and anuria for thirty-six hours. The local physician had seen the child on the second day of illness, diagnosed Vincent's infection of the mouth, and had prescribed symptomatic and supportive therapy. Because of no improvement in three days, he swabbed the child's mouth with one-half per cent bismuth violet solution and injected intramuscularly one-eighth of the contents of an ampule of thio-bismol,* a dosage equivalent to 10 mg. of metallic bismuth. Within twenty-four hours

From the Department of Pediatrics, North Carolina Baptist Hospital and Bowman Gray School of Medicine, Winston-Salem, N. C.

*Sodium bismuth thioglycollate, 0.2 Gm., to be dissolved in distilled water.

the child had ceased to void. On the following day (sixth day of illness) the physician catheterized her, but obtained no urine from the bladder. The patient was then referred to this hospital where she was admitted, thirty-six hours after the last urination.

Physical examination revealed an acutely ill infant in semicoma. She could be roused by stimulation but was fretful and irritable. Temperature was 98° F.; pulse rate, 130; respirations, 24; and blood pressure, 118/88. Both eardrums were slightly reddened. The gums and mucous membranes of the mouth were swollen, ulcerated, and bleeding. There was a foul odor to the breath. The bladder and other abdominal organs could not be palpated. Dehydration was not evident. The remainder of the physical examination revealed nothing contributory.

Examination of the blood revealed 12 Gm. hemoglobin, 4.8 million red cells, and 12,000 white cells per cubic millimeter. Blood nonprotein nitrogen was 76 mg. per hundred cubic centimeters and the carbon dioxide combining power was 31 volumes per cent. A smear from the gums revealed fusiform bacilli and spirochetes. Kahn test was negative.

The child was given 200 c.c. of 10 per cent glucose in saline intravenously immediately upon admission, was started on nicotinic acid, 50 mg. three times a day, and the mouth was washed with sodium perborate solution at frequent intervals. Fluids were forced orally. Twelve hours later the child was catheterized; no urine was obtained. A constant drip was then started, and over the next eighteen hours the child received 1,300 c.c. of intravenous fluids. The next morning (third hospital day) the blood chemistry was essentially as on admission. (Chart I.) The child had not voided. Two cubic centimeters of aminophyllin were given intravenously without effect. Six hours later 40 c.c. of 25 per cent glucose with 4 c.c. of aminophyllin were given intravenously. The child continued to be drowsy and was beginning to vomit occasionally.

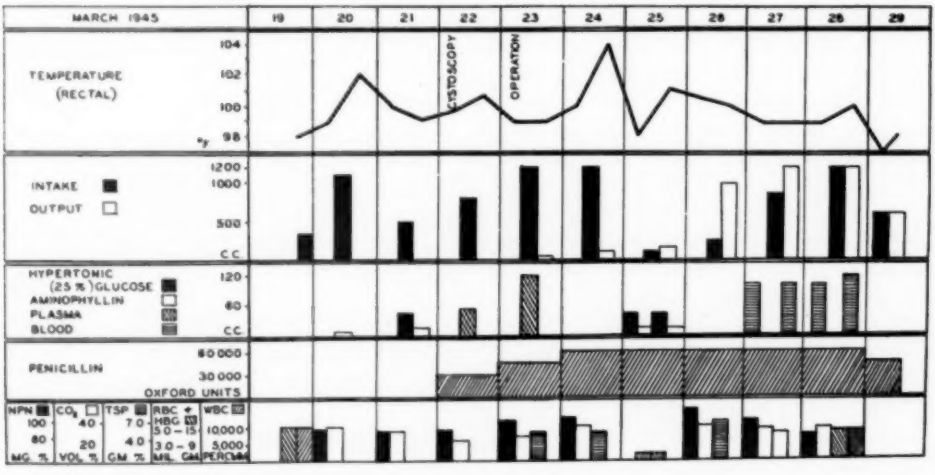


Chart I.

On the fourth hospital day (sixth day of anuria) the patient was cystoscoped and ureteral catheters were passed. A small amount of urine (from 1 to 3 c.c.) was drained from each renal pelvis, but after this was obtained no more flowed from the catheters. This urine contained no cells and was sterile on culture. While the cystoscope was in place, retrograde pyelograms were made, revealing a bifid ureter on the left and a normal ureter and kidney pelvis on the right. Following this she received 500 c.c. of 10 per cent glucose in saline intravenously, and her general condition continued unchanged. Blood nonprotein nitro-

gen remained at the same level. Because of the possibility of the anuria being on an infectious basis, the child was started on penicillin, 5,000 units intramuscularly every two hours.

On the fifth hospital day the patient still had not voided, and her general condition seemed worse. Nitrogenous retention in the blood was increasing. (Chart I.) In view of the seriousness of the situation, decapsulation of the kidneys was deemed advisable. Under ether anesthesia, the kidneys were exposed. A bifid ureter on the left and an aberrant vessel

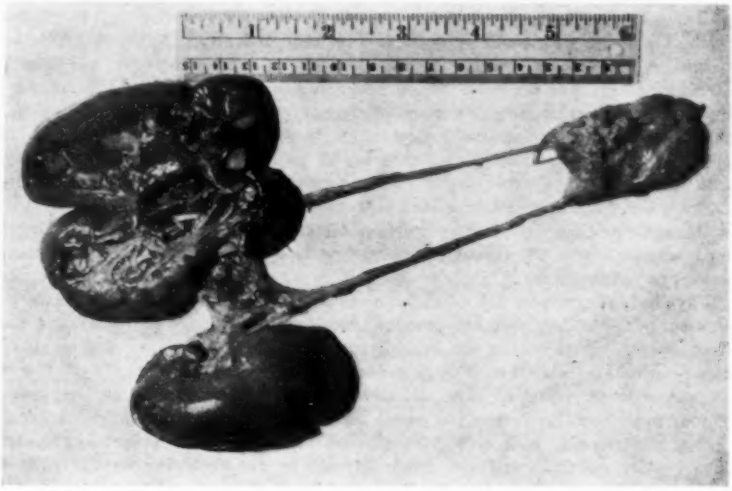


Fig. 1.—The kidneys at post-mortem examination, with the left kidney opened to show the areas of infarction in the lower pole.

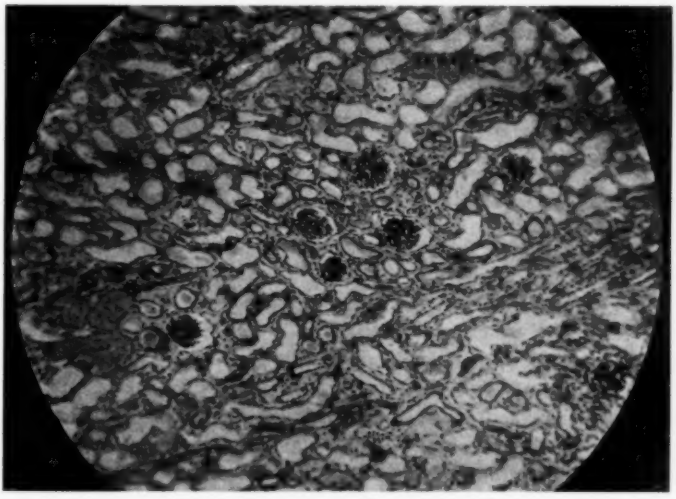


Fig. 2.—Photomicrograph of section of kidney showing widespread tubular degeneration (×170).

across the lower pole of the left kidney which almost divided this portion from the main body of the kidney were found. The aberrant vessel was ligated and cut, and the capsules of the kidneys were stripped loose with ease. Over the following twelve hours the child received intravenously 800 c.c. of fluids and 200 c.c. of plasma.

Immediately postoperatively the infant remained essentially as before with the exception that 5 c.c. of grossly bloody urine was obtained from the bladder by catheterization. Fluid intake was maintained by means of the intravenous route and hypertonic glucose solution was injected on two additional occasions. Edema of moderate degree formed in the face and dependent portions of the body. On the fourth postoperative day the infant appeared definitely worse and could be roused only with difficulty. An examination of the blood revealed only 5 Gm. of hemoglobin and 1.6 million red cells per cubic millimeter, with a hematocrit of 14 volumes per cent. Blood nonprotein nitrogen was now 123 mg. per cent, but the other chemistries were in the range of normal (Chart I). Over the following three days four transfusions, totaling 420 c.c. of whole blood, were given intravenously, raising the hemoglobin to 11 Gm. and the red cells to 4.0 million per cubic millimeter. Concurrently with this therapy the infant began voiding small amounts of bloody urine on frequent occasions, and her general appearance was that of improvement.

On the sixth postoperative day (tenth hospital day) the blood nonprotein nitrogen was down to 61 mg. per cent. The infant was taking fluids well orally and was voiding approximately once every four hours. Urinalysis revealed an alkaline specimen with 1 plus albumin, occasional hyaline and granular casts, and an occasional white cell. The edema of the patient was subsiding. It was felt that her general condition was greatly improved and that recovery was assured. However, on the evening of that day she developed a generalized erythematous, petechial, macular rash with generalized increased capillary fragility. The tourniquet test was strongly positive. The abdomen became distended, and the liver edge was palpable four fingerbreadths belows the costal margin. The infant presented the picture of one in peripheral vascular collapse. Adrenal cortical extract therapy was begun, but the course was rapidly downhill, and the infant expired on the following day in spite of all supportive measures.

At post-mortem examination confluent areas of ecchymosis were noted over the body and extremities. There was mild edema. The kidneys were pale, but did not appear enlarged; the right organ weighed 70 grams and the left weighed 75 grams. The capsules were absent. A bifid ureter was present on the left, and there was infarction in the lower pole of the left kidney from which the aberrant vessel had been cut (Fig. 1). Microscopically, sections of the kidneys showed mild fragmentation of the glomeruli and lymphocytic infiltration into the interstitial spaces, but the major pathology was widespread tubular degeneration. The tubules were dilated, filled with granular material, and the epithelium was markedly damaged (Fig. 2). In addition, there was congestion of the liver, spleen, and lungs, and pulmonary edema with bronchopneumonia.

Chemical analysis of the renal tissue revealed the presence of 0.5 mg. of bismuth, determined by the method of Sproull and Gettler.[6] This was 5 per cent of the original amount still present fourteen days after injection and five days after restoration of renal function.

COMMENT

The renal damage in the case presented was a toxic (necrotizing) nephrosis due to the presence of bismuth, as confirmed by chemical analysis. The tubular epithelium was mainly affected with little change in the glomeruli, which is the condition usually found with toxicity due to the heavy metals. It is felt that the aberrant vessel present in this case was of incidental occurrence, and that it played no part in the anuria. The blood in the first urine specimens obtained was, in all probability, due to the trauma associated with decapsulation. When regular flow of urine was re-established, there was a moderate amount of albumin and a few casts, with a small number of cellular elements, which is the condi-

tion one would expect in patients recovering from bismuth nephrosis. This improvement continues over a variable period of time until normal renal function is restored.

Toxic signs other than anuria, such as nausea and vomiting, diarrhea and drowsiness, may or may not be manifest. Uremic symptoms appear if kidney function is not soon restored. Blood pressure may or may not rise and is usually low in the presence of anuria. Edema is uncommon until the late stages.

It should be stressed that care is essential in the administration of bismuth, or any heavy metal, to a child. The urine must be watched carefully, and any deviation from normal should be a signal for discontinuance of the drug. Nephrosis, if it occurs, is best treated by the administration of intravenous fluids and hypertonic glucose solution. Whole blood and plasma are used as indicated to combat anemia and hypoproteinemia. Vasodilators, such as caffeine, aminophyllin, or theobromine, may be tried without causing further damage. Surgical procedures, in the form of ureteral catheterization, are in order to rule out mechanical blockage of the urine flow, but decapsulation of the kidneys should be used only as a last resort.

I wish to express appreciation to Dr. Jean Bailey, of the Department of Pathology, for her help in the post-mortem examinations, and to Dr. William A. Wolff, Chemist, for the bismuth determinations.

REFERENCES

1. Eitzen, A. C.: Am. J. Syph., Gonor. & Ven. Dis. **21**: 674, 1937.
2. McClendon, S. J.: Am. J. Dis. Child. **61**: 339, 1941.
3. Goodman, Louis, and Gilman, Alfred: The Pharmacological Basis of Therapeutics, New York, 1941, The Macmillan Company, p. 978.
4. Masson, George A.: J. Pharmacol. & Exper. Therap. **30**: 121, 1926.
5. Leonard, Clifford S.: J. Pharmacol. & Exper. Therap. **28**: 89, 1926.
6. Sproull, R. C., and Gettler, A. O.: Ind. & Eng. Chem., Anal. Ed. **13**: 462, 1941.

VERTEBRAL HEMANGIOMA IN CHILDREN

IRA I. KAPLAN, M.D., B.Sc.
NEW YORK, N. Y.

THE usual hemangioma seen in children referred for irradiation is the superficial lesion or birthmark on the skin. Hemangiomas are congenital to quote Ewing[1] "of early development, slow in growth and benign in course." Such as appear on the face are most readily recognized and usually attended to early for cosmetic reasons. The less common hemangioma is that involving bone, whose symptoms resemble various other conditions, and where only the x-ray examination suggests an hemangioma by reason of the characteristic striated effect. The child usually complains of pain in the back and gradually exhibits signs of functional disturbances of the limbs. During the past two decades there were but five cases of bone hemangioma referred for treatment to the Radiation Therapy Department at Bellevue Hospital, and the case reported herein is the only one in a child with vertebral involvement.

Geschickter and Copeland[2] report that the number of verified cases of bone hemangiomas is small. In most instances their finding is incidental to examination following trauma or in cases involving the spine when neurological symptoms demand attention. The x-ray shows a characteristic soap-bubble effect.

Friedman[3] describes as follows the x-ray appearance of hemangioma of bone: "Benign angioma in bone is revealed in the early stages as a circumscribed area of rarefaction; later, the presence of coarse striations and, at times, loculations is also observed. The tumor in flat bones is usually revealed by the characteristic "sunburst" trabeculations radiating from a common center. The lesion in tubular bones may cause cortical destruction but no periosteal perforation, hence the tumor is well circumscribed even beyond the confines of the involved bone."

According to Blackford,[4] "Hemangiomas of the vertebrae have been noted in more than 10 per cent of a large series of routine autopsies, more commonly in older persons and in females." X-ray reveals coarse, vertical striations and trabeculations which may extend to the pedicles. The vertical diameter of the body of the vertebra and the intervertebral spaces are not disturbed. Symptoms are due not so much to the presence of hemangioma as to the encroachment on the spinal canal, with effects due to compression of the cord. When they occur in young males, Blackford says, they seem to cause symptoms relatively often. He also states that when symptoms suggest tumor of the spinal cord possibility of hemangioma of the vertebrae should be borne in mind.

In cases of hemangioma of the vertebrae, if diagnosis is made before irreparable damage to the cord has taken place irradiation may be expected to effect a cure and Blackford reports cures in twelve cases treated by irradiation

From the Radiation Therapy Department, Bellevue Hospital, New York University College of Medicine.

alone and reports favorable results in a young man treated fourteen years previously so successfully as to be able to assume active duty in the Army.

The following case is one of angioma of the vertebrae.

E. L., a white boy, aged 12½ years, was admitted Oct. 2, 1943, to the neurological service of Bellevue Hospital because of increasing numbness of the legs with weakness and loss of function of eight weeks' duration. Temporary diagnosis of a spinal new growth

Fig. 1.—X-ray of involved vertebrae, Oct. 6, 1943.

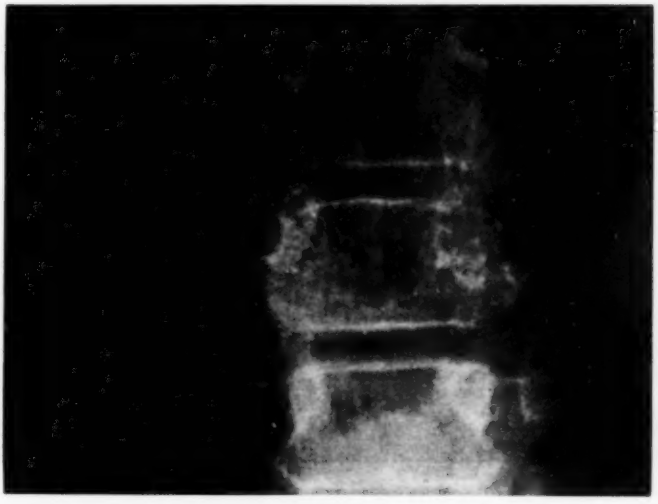


Fig. 2.—X-ray of involved vertebrae after treatment, Feb. 24, 1944.

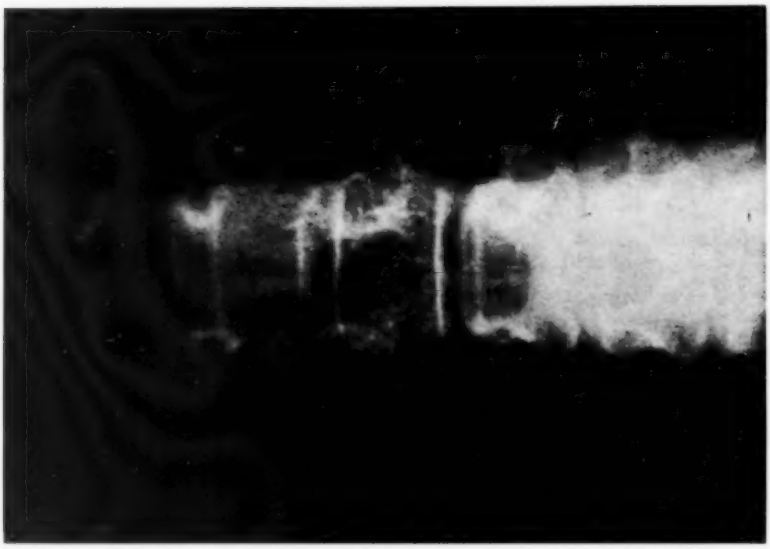


Fig. 4.—X-ray of the spine taken six months after last visit, Sept. 24, 1945.

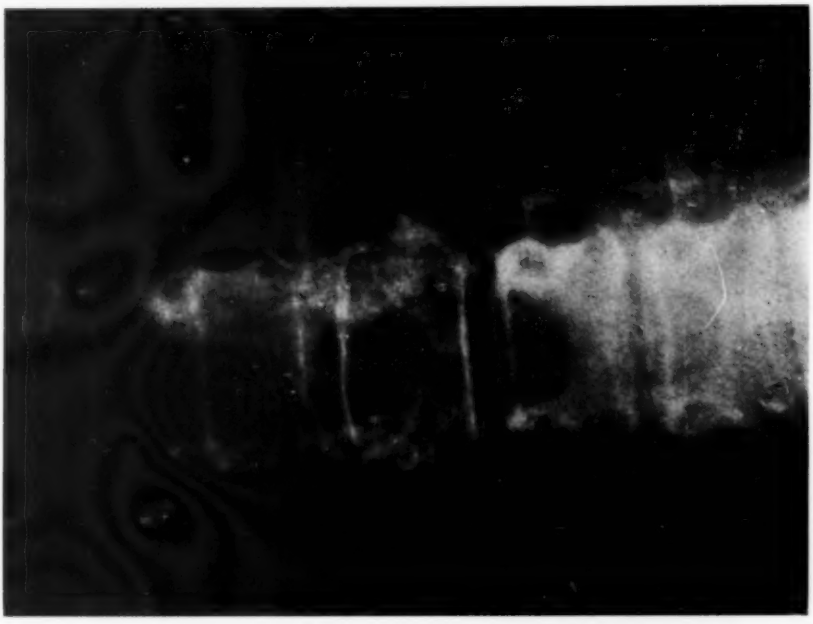


Fig. 3.—X-ray of involved vertebrae after treatment, March 20, 1945.

was made, but the x-ray at this time was suggestive of hemangioma (Fig. 1). On Oct. 9, 1943, a laminectomy was performed at the level of the third to the sixth dorsal vertebrae. A section of tissue was removed for biopsy and the pathology proved the lesion to be a hemangioma. At this time there was complete inability to move the legs and some pain in the spine. He was referred to the Radiation Therapy Department for further treatment and on Oct. 27, 1943, x-ray therapy was started and continued until Nov. 9, 1943. High voltage x-ray filtered through 0.5 copper was administered and 2,000 r was given over the area of the fourth to the eighth dorsal vertebrae. Slight improvement followed. On Jan. 19, 1944, after a second course of x-ray administered from Jan. 6 to 19, 1944, with 2,000 r given, noticeable improvement followed. From Feb. 24, to March 13, 1944, another course of x-ray therapy was given, directed at the anterior vertebrae areas through the mediastinum; 600 r was administered. From April 13, to May 31, 1944, x-ray therapy of a dose of 1,500 r was administered. X-ray examination on Feb. 24, 1944 (Fig. 2), still showed the striations in the vertebrae, but the condition of the boy was markedly improved; he was able to stand and walk without difficulty, and there was no interference with skeletal growth. X-ray examination on April 6, 1944, showed no essential change in the appearance of the body of the fifth dorsal vertebrae. The clinical condition, however, gave evidence of regression and healing. The patient was up and about, walking without difficulty and in a happy mental state. There is no evi-

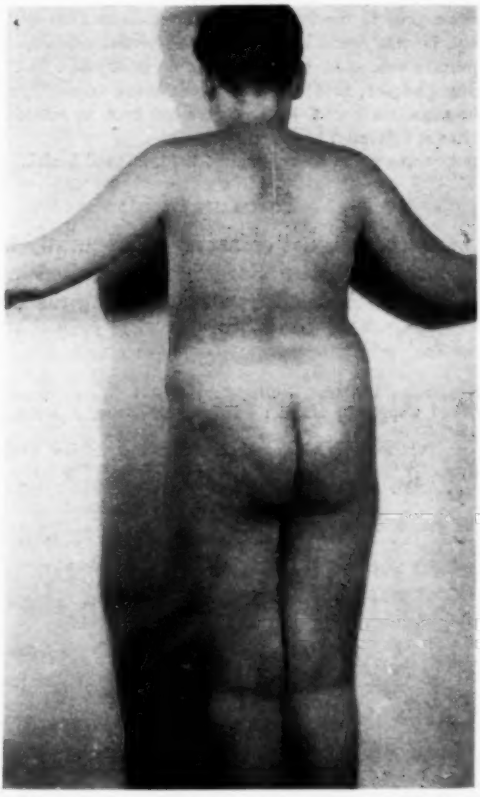


Fig. 5.—A picture showing present condition, healed scar, and straight back of the child following operation and treatment.

dence of paralysis in any part of the body. (Not always in cases of bone lesions does definite change appear in the x-ray film, though clinical improvement is quite marked. This explains the similarity in the roentgenographs before and after treatment in this case.)

The patient was discharged home and kept under observation. In March, 1945, roentgenograms were again taken of the spine and a moderate resolution of the lesion was noted, there was increased density, probably due to the deposition of calcium from irradiation.

Examination of the boy on April 26, 1945, revealed a good general condition with gain in weight. He walked well without assistance, and had no complaints.

Because of the picture of residual involvement in the affected vertebrae further x-ray therapy was advised and during the period April 26, to June 1, 1945, 1,000 r of high voltage x-ray therapy was administered to the involved dorsal vertebrae area.

On June 11, 1945, he was again examined. His general condition was excellent; there were no complaints, posture was good, and there was no paralysis.

At time of writing (August, 1945) the lad was at home, free of symptoms, happy, lively, and carrying on in the usual manner of boys. There has been no retardation of body growth and he stands erect without difficulty.

Addendum.—The boy was again seen January, 1946, in good health.

SUMMARY

Hemangioma of the bone is not common. It frequently involves the spine. Irradiation is the method of choice. Surgery is recognized in some cases to relieve pressure on the cord. A case is reported showing the favorable results of treatment.

REFERENCES

1. Ewing, James: Neoplastic Diseases, Philadelphia, 1934, W. B. Saunders Company.
2. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, American Journal of Cancer, New York, 1931.
3. Friedman, Lewis J.: Textbook of Diagnostic Roentgenology, New York, 1937, D. Appleton-Century Co., Inc.
4. Blackford, L. M.: J. A. M. A. 123: 144, 1943.

The Social Aspects of Medicine

I wrote Professor Lichtenstein several months ago asking him if he would not write an exposition of the Swedish system of medical care, with his criticisms, for the JOURNAL OF PEDIATRICS.

I think that every member of the Academy ought to read it in order that he may become conversant with the system of medical care in another part of the world. I shall try later to obtain expositions of the system of medical care now in operation in England and of the one in New Zealand.

E. A. P.

THE SYSTEM OF MEDICAL CARE OF CHILDREN IN SWEDEN

A. LICHTENSTEIN
STOCKHOLM, SWEDEN

Sweden is one of the smaller countries of Europe as regards population, the number of inhabitants on Jan. 1, 1945, being 6,597,348. In area, however, (449,000 square kilometers) the country is relatively large, somewhat smaller than France and nearly 50 per cent larger than Great Britain and Ireland. The country is, therefore, in parts very sparsely populated. Industrialization has led to an increasingly large influx into the cities. This is shown by the following figures:

CITY INHABITANTS IN PER CENT OF THE WHOLE POPULATION OF SWEDEN

Year	1840	1860	1880	1900	1920	1940	1945
Per cent	9.67	11.26	15.12	21.49	29.40	37.24	41.49

Sweden is divided into twenty-four counties. The six largest towns do not belong to any county but have their own independent administrations. These towns are: Stockholm, with a population of 654,864; Gothenburg, with 309,348; Malmö, with 167,885; Norrköping with 75,792; Hälsingborg, with 65,375, and Gävle with 40,988. All these figures are for Jan. 1, 1945.

Medical Training.—Medical training is long and thorough, and takes, as a rule, from eight to ten years after matriculation (Studentexamen) which is usually taken between the ages of 18 and 20. Medical training is paid entirely by the state. Apart from certain special courses, medical students do not pay any fees for instruction, which means that even those of limited means can study medicine. Every medical student does a three-month course in pediatrics, which has been an obligatory examination subject for more than one hundred years.

Specialist Training.—Specialist training takes, in most cases, at least three years. Due to an insufficiency of salaried posts, specialist training cannot, as a rule, be started before from two to five years after the qualifying medical (Licentiate) examination. In order to advertise as a pediatrician, three years at least of hospital training at a children's hospital are required, or, as an alternative, at least two years' similar training in addition to a third year which can be devoted entirely to internal medicine or epidemiology, and partly to other fields of medicine important to a pediatrician, such as pulmonary tuberculosis, otology, orthopedics, psychiatry. The number of qualified pediatricians is for the moment only about 120.

The Control of the Health Service and Medical Care.—The control of the health service and medical care is entrusted in Sweden to the Medical and Health Board, organized in dif-

ferent medical bureaus for hospitals, medical practice, hygiene. The Board is assisted by a scientific council composed of members representing different specialities, medicine, surgery, pediatrics, child welfare.

The Treatment of Inpatients.—The treatment of inpatients is cared for by hospitals, owned and operated by the county councils or, in the case of the above-mentioned six towns by their municipal authorities, with the help of taxation. As a rule, only the university clinics are built by the state, partly in cooperation with the counties or, in Stockholm, with the municipal authorities. The care of the physically sick devolves therefore upon the local authorities. The institutions for the care of the mentally diseased, on the contrary, are mostly built by the state.

It is our aim to have a central hospital with special departments of all kinds in every county. The care of sick children was, however, for a long time neglected by the state and the municipal authorities, and was cared for by private charities. Nowadays, however, children's hospitals and children's wards in the hospitals are built by the counties, with the aid of state contributions both for the actual building and for maintenance, at a rate based on the provision of two hospital beds for children per 10,000 inhabitants. Besides these children's wards in the county hospitals, there are university clinics (two in Stockholm, one in Upsala, and one in Lund), as well as children's hospitals or children's wards in each of the above-named six larger towns. At the present moment, the number of children's hospitals and children's wards in Sweden is twenty-four, with altogether about 1,300 beds. A number of new children's wards are planned and are partly in the process of building.

Care at the county hospitals is intended, in the first place, for those actually resident in the county. At the university clinics and to a certain extent at other children's hospitals, patients are accepted from any part of the country. State contributions to the maintenance make it possible for the costs to the patients to be kept on a very low level. As a rule, the cost per day at a children's hospital is 1.50 Swedish crowns (about 40 cents). These costs, which include x-ray and other special examinations, are paid for entirely by the sick relief funds for their members. The remainder of the actual cost, which amounts to from eight to ten times more than the sum actually paid by the patients, is taken care of by the principals of the hospitals and, in the case of children, with the help of state subsidies.

Sick Relief Funds.—Since 1931, the sick relief funds are regulated by the state. Those contributed to by the state are known as approved sick relief funds, and are under state control. Such a sick relief fund is legally bound to accord to its members certain minimum advantages in the form of sick pay and maternity help. Due to state subsidies, the contributions of members to the funds can be kept very low, which allows even those with very low incomes to become members. The benefits offered by an approved sick relief fund are therefore considerably higher than those corresponding to the contributions paid into the fund.

Sick pay consists partly of compensation for medical care for the direct costs of the sickness (for medical attendance a maximum of two-thirds of the cost, and for hospital treatment the entire costs in a public ward), and partly of sick pay, which constitutes a certain compensation for partial or total loss of earned income due to inability to work during the period of sickness. This is calculated at a fixed sum per day.

Since the compensation for medical attendance is calculated at two-thirds of the cost, according to a fixed so-called "medical care scale," intended only to regulate the financial relations between the insured person and the sick relief fund and not as a binding scale of charges for the doctor, it carries with it the important advantage both for the patient and for the doctor, that the patient can be attended by the doctor of his choice, even if he is a specialist with relatively high fees. In the latter case, however, the insured person must himself contribute a larger sum of money than were he to be attended by a general practitioner.

Maternity aid, which is given to every woman member of the sick relief fund when she is confined, consists of a cash sum of money, at present at least 110 Swedish crowns (as a rule, 125 Swedish crowns).

Entry into the sick relief fund can, as a rule, take place between the ages of 15 and 45. A member who registers his or her healthy child under the age of 15 years can

have him insured as a general rule without a special fee. For such a child, compensation for medical care is given in the case of sickness.

At the end of the calendar year 1943-1944, 2,147,174 persons were members of approved sick relief funds, a figure corresponding to 41.5 per cent of the population of the country over the age of 15 years. At the same time, 763,184 children were insured through the membership of their parents, corresponding to 56.4 per cent of the children of the country under the age of 15.

The sick relief fund movement, of which membership has hitherto been voluntary, has, it is true, spread widely, and the number of members has increased very rapidly. In spite, however, of the relatively low contributions to be paid, a large number of those who are worst off financially are still not members. The Government, after an investigation which has already been carried out, now intends to propose a general obligatory sick relief fund insurance for everyone, a project which seems likely to be enforced in the very near future.

The Senior Medical Officers.—The senior medical officers of hospitals are appointed by the state at the suggestion of the Medical and Health Board. These doctors are either appointed for the entire period until retirement with pension (which in Sweden is 65 years of age) or for a certain period (as a rule from five to ten years), in which case the appointment is usually renewable until the age of retirement is reached. Chief medical officers can, therefore, in practice not be dismissed unless they commit some serious error in the discharge of their official duties, or a breach of the common law.

House Physicians and Assistants.—House physicians and assistants are appointed by the principals of the hospital in question, usually for a period of from one to five years. The appointments can, as a rule, be renewed once, or even several times. Due, however, to the lack of a sufficient number of salaried appointments, there is at present a tendency to try to limit the years of appointment for house physicians and assistants, and at the same time to create assistant Chief Medical Officers posts which can be held for a longer period.

The doctors appointed at the hospitals are paid by the principals of the hospitals. The Chief Medical Officer is responsible for the examination and treatment of the patients admitted to the hospital and also for the reception and treatment of patients in the dispensary. In the latter case, the fees to be paid, partly voluntarily and partly through agreement, have been fixed so low that it is possible for practically any sick person to visit a specialist. The sick relief fund pays a certain part of the doctor's fees for its members. Besides his hospital work, the specialist has the right to private practice and is, in this instance, not bound by any fixed scale of fees.

In the children's hospitals in the larger cities there are, as a rule, outpatient departments where persons of little or no means can receive specialist treatment at a very small fee, usually paid by the sick relief fund. This fee is, as a rule, about 1 to 2 Swedish crowns per visit (from 25 to 50 cents), and no fee is charged if a so-called social certificate of lack of means is produced.

The Care of Outpatients.—The care of outpatients is given in large cities by pediatricians and in the countryside by practicing doctors and provincial public health officers. The two latter groups of doctors have, as a rule, no very extensive pediatric training.

The Pharmacy System.—The pharmacy system in Sweden is based upon personal concession by the Government to a vacant pharmacy. The sale of medicines, especially of poisons, is in general restricted to the pharmacists. The supervision is vested in the Medical Board, which also fixes the prices of medicines by a tariff issued once a year.

Prophylactic Treatment.—Prophylactic treatment begins with prenatal care during pregnancy. This is given partly at maternity centers and partly by private physicians.

Confinements.—Confinements take place in a rapidly increasing degree at maternity hospitals. While in 1930 only 24 per cent of births took place at maternity hospitals, the figure had risen in 1940 to 65 per cent, and in 1943 to 73 per cent.

The care of infants and sick infants at the maternity hospitals has for long been unsatisfactory, on account of unsuitable premises and a lack, both quantitative and qualitative, of suitable personnel for their care.

It is only recently that pediatricians have been given the opportunity of working on a large scale at maternity hospitals. At the present moment, in Stockholm, for example, a pediatrician is appointed at every maternity hospital, with the task of supervising the care of the infants and of treating sick infants there.

Sweden has, since 1937, a state organization of maternity and child welfare centers covering the whole country. These are organized as follows: Maternity centers of Type I and child welfare centers of Type I are under the charge of, respectively, a specially trained obstetrician or pediatrician, as a rule the chief medical officer of a department of the hospital, with a full-time nurse to help him. Corresponding centers of Type II are designed for towns and closely populated areas without access to specialists. Type III are known as maternity and child welfare stations and are spread over the whole country. At these stations, the care of the mothers and children is entrusted to the provincial medical health officers, with the aid of the district nurses and district midwives.

In 1944, there were 26 maternity centers of Type I, 77 child welfare centers of Type I, 33 maternity centers of Type II, 31 child welfare centers of Type II, 31 combined maternity and child welfare centers of Type II, and 416 combined maternity and child welfare stations (Type III) with 587 affiliated branches. The sum total of maternity and child welfare centers was, in 1944, 1,193, and the number of surgeries held 45,601.

Care at maternity and child welfare centers is entirely free of charge. Where necessary, prophylactic medicines, cod-liver oil, calcium and similar supplies can be requisitioned free, and are paid for by the state. Only health care can be obtained at the child welfare centers, but at the maternity centers, sicknesses are also treated.

Health control at child welfare centers is entirely voluntary, but attendances must be considered as good. Of 133,167 children born in 1944, 106,899 were under control, a figure which corresponds to 79 per cent. In certain of the larger towns, the percentage under control is even higher. For example, in Gothenburg, the figure is 90 per cent, and in Norrköping, nearly 90 per cent.

This care covers the first year of life. We are endeavouring to place children over the age of one year under the control of the centers. In Stockholm and Gothenburg, all children to the age of entering school already have this possibility. In other parts of the country, children to the ages of 2 to 3 are under control. The organization already described is in the process of rapid development. The lack of a sufficient number of trained pediatricians and insufficient pediatric training for state-appointed public health officers, constitutes a certain difficulty in the growth of the plan. An improvement in this situation is under way.

Health Care of Children of School Age.—Health care of children of school age is entrusted to the school doctor, who is assisted by a school nurse. The system of school doctors, which has for a long time left much to be desired, has now an organization covering the entire country. The aim is to place every child at school under the care of a competent school doctor. Training in pediatrics is, as a rule, a deciding factor in the appointment of a school doctor.

Mental Care in Schools.—Mental care in schools is rapidly increasing. Preventive and medical mental care of children is at present also organized by the State. We aim at having as a leader of this activity a child psychiatrist in each county, assisted by a psychologist and social assistants. This organization however, has only hitherto been practiced on a very small scale.

In the largest cities there are special advisory bureaus to deal with questions of child guidance. Children who have educational difficulties and difficulties of adaptation are also accepted in large numbers at the children's clinics for more thorough investigation.

Care of Handicapped and Others.—The care of the blind, the deaf and dumb, invalids, epileptics, and mentally deficient is taken care of by special organizations. A description of the activities of such organizations would take up too much space here. The costs of such care are borne partly by the state and partly by the municipalities by means of taxation.

CONCLUSIONS

Child mortality in Sweden is low and is continually on the decrease. In 1900, infant mortality was 7 to 8 per cent; in 1930, 6 per cent; in 1940, 4 per cent; and in 1944, 3 per cent. The neonatal mortality (death in the first week after birth) has, however, decreased only very slightly, and today constitutes, therefore, a higher percentage of infant mortality than previously. It is hoped, through improved care during confinement, and more efficient care of the newly born child, under the supervision of pediatricians, to decrease the early infant mortality. At the moment, special interest is paid to the care of premature infants. They are taken care of, in an increasingly greater number, at children's hospitals.

As can be seen from this account, we have in Sweden a combined system of state and private medical care. The state and the municipality, partly with the help of the sick relief funds, ensures that every sick person, irrespective of his financial situation, has the opportunity of obtaining the best possible medical care either in the hospitals or outside. To this end, the best specialists in the country in various fields are available as salaried medical officers at hospitals and as doctors for outpatients. The patient has, to a great extent, a free choice of physician. *In my opinion, the free choice of a physician is necessary, for the patient, and for the physician, even in the case of members of sick relief funds, which embrace the largest proportion of the country's population.* The medical profession in Sweden is free, so that the individual doctor can, within a wide boundary, of his own free will choose the place and type of his activities. Even doctors appointed by the state or the municipalities are entitled, in so far as their work at the hospital permits, to carry on their profession with complete freedom.

This system has, in my experience, functioned well, and on the whole fulfills the wishes of both the patient and the doctor. It is my opinion that a substantial state subsidy and control is necessary, if the health and care of the sick in a country are to function effectively and satisfactorily. The fears expressed by some doctors, that a state activity as regards medical care would hamper or prevent the practicing doctor's exercise of his profession, have proved themselves to be unjustified. On the contrary, the work, for example, of the child welfare centers has increased the interest of the public in child welfare and the care of sick children, and private pediatricians are sought in an ever-increasing degree. Such a development, however, presupposes that the state medical activities are not so organized as to make private medical practice impossible. *I fear that should medical activities be entirely controlled by the state, this would, in all certainty, lead to an unfortunate medical bureaucracy and also to an elimination of the personal contact between the patient and the doctor, which is a necessary condition for all good medical activity.* Such a socialization would mean, for the medical profession, a lowering of the standard which is in direct opposition to the interests of the country. *The duty of the state, is, however, to organize medical care in such a manner that every person, irrespective of his income, can procure the best preventive and curative medical care.*

In my opinion, the Swedish system shows very clearly that this can be done without undermining private medical practice.

January 24, 1946

Dr. Edwards A. Park
Johns Hopkins Hospital
Baltimore 5, Maryland

Dear Doctor Park:

I am enclosing a letter which I have written and on which I would like to have your opinion. I have gotten into this discussion rather unwittingly because Dr. White, who is President-Elect of the New York County Medical Society, asked me for my opinion. If you want to use this for your column in the JOURNAL OF PEDIATRICS you are free to do so.

With kind regards, I am,

Sincerely yours,

ALEXANDER T. MARTIN, M.D.

January 3, 1946

Dr. Roy B. Henline, President
New York County Medical Society
2 East 103rd Street
New York City

Dear Doctor Henline:

B. W. has asked me to comment on this small pamphlet *Stepping Stones to Regimentation* prepared by the Maternal and Child Welfare Committee of one of our State Medical Societies. In my opinion it represents a type of thinking which does no credit to our profession and which, I regret to say, is shared by an articulate group which is in control of medical policy in many of our State Societies. This is also reflected in the thinking of the parent body. Many of them still belong to the horse and buggy era and are willing and desire to carry on business as usual. They do not "discern the signs of the times" (a Scriptural injunction) and they are impervious to and insensitive toward the vast movements which have been set in motion by the cataclysm of the recent war. Too often has our profession been destructive rather than constructive in its cirticism. "Too late and too little" may be the indictment which will be lodged against us.

The Pepper bill, S. 1318, to which the pamphlet directs itself, is not perfect but its main objectives are excellent. I do not believe that there will be infringement on private practice as is feared by many. I do believe that the main purposes of the bill will provide better distribution and more adequate medical care which will be available to families in the lower income brackets. Whether a "means test" should be applied is still a matter of debate and difference of opinion. I would hope that the economic aspects of the medical care program would not obscure the service aspects. Those who maintain that the EMIC Program has been set up by the Children's Bureau as a "trial balloon" are "straining at a gnat" and are suffering from a "blind spot." The Bureau has reiterated time and time again that the EMIC Program is an emergency measure which ends six months after the war terminates. No physician was regimented, as the Pamphlet states, but each was free to accept or reject any patient who applied for care. To the credit of the medical profession over one million wives of our fighting men were taken care of. This gave a tremendous lift to morale and gave a feeling of security to the men in the services.

Much has been said about the self-appointed Advisory Committees by the Children's Bureau and the intimation made that the Committees, being without power, only advise or recommend what the Bureau directs. This is far from the facts. In my opinion, the Advisory Committees have been well chosen and the recommendations by these Committees have been, in the main, approved and accepted by the Children's Bureau and have been incorporated in their Health and Welfare Programs. The members of these Committees have not been the tools of the Children's Bureau but, by frank discussion, have brought to the Bureau a wealth of wisdom and experience.

And so, it is only by frank discussion, constructive criticism and mutual understanding that we can arrive at a solution to the complex problems of medical care. "Rome was not built in a day" and the Pepper bill, S. 1318, will probably be amended many times before its final writing. Its final form will depend on how much "collective agreement" we can bring to it.

The American Academy of Pediatrics has shown progressive leadership and cooperation with governmental agencies. Even now, the Academy is making a two-year survey of child health services with the cooperation of the United States Public Health Service and the Children's Bureau. This survey was initiated and is being conducted by pediatricians in the Academy, and its main objectives are four:

1. Pediatric education
2. Distribution, qualifications and activities of professional personnel
3. Hospital facilities, including out-patient clinics and laboratories
4. Health services for children.

I would stress the fact that this comprehensive survey is being made by physicians themselves and could be a model for other professional groups to follow.

The pamphlet *Stepping Stones to Regimentation*, which has provoked this discussion, does a disservice to the profession. We should set our sights higher. If we do not, we will miss the boat.

ALEXANDER T. MARTIN, M.D.
107 East 85th Street
New York City.

Dear Dr. Park:

In recent years a number of bills have been introduced in Congress and in State Legislatures which would authorize the appropriation of considerable sums of money to finance Medical Care Programs. There has been considerable criticism and opposition to these bills on the basis that they would result in a government dominated medical profession, and that this would mean a poor type of medical care.

It is generally accepted that there is a considerable group of the population, perhaps one third, which cannot afford to purchase the medical care which they need. It is also recognized that voluntary insurance plans can hope to provide care only to those individuals in families with sufficient incomes to pay the insurance premium. This leaves the indigent and medically indigent groups still to be provided for.

Most of the criticism of pending medical care bills has failed to offer alternative suggestions which would meet the need. In order to obtain further constructive thinking on these points, will you ask pediatricians to send suggestions to your column as to ways in which public tax funds could be used to bring medical care of high quality to the masses of the population who need it.

Very truly yours,

DEAN ROBERTS

News and Notes

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. G. E. Harrison, Mason City, Iowa
Dr. J. Herbert Young, Boston, Mass.

Dr. Harrison S. Collisi, who retired from the United States Army with the rank of Colonel in December, 1945, has been named medical director of the Planned Parenthood Federation of America, Inc.

The Michael Reese Hospital Post-Graduate School with the cooperation of the members of the Department of Pediatrics, University of Chicago, and Loyola University School of Medicine, will offer a course in Pediatrics. The course will be held at Michael Reese Hospital from May 1 to May 29, 1946; full time; tuition, $100. Write to Dr. Samuel Soskin, Dean, Michael Reese Hospital Post-Graduate School, Twenty-ninth Street and Ellis Avenue, Chicago 16, Ill.

The Pediatrician and the War

Promotions of the following Fellows have been reported to the JOURNAL:

Captain William T. Ball, Charleston, S. C., to Major
Lieutenant Colonel Lewis Webb Hill, Boston, Mass., to Colonel

Colonel Warren C. Fargo, Cleveland, Ohio, has received the Legion of Merit Medal for his work at Fort Sam Houston.

The following Fellows have been released from the Armed Services:

Dr. Charles E. Anderson, Jr., Shreveport, La.
Dr. George E. Anthony, Flint, Mich.
Dr. Lawrence C. Bachmann, Pittsburgh, Pa.
Dr. William J. Ball, Charleston, S. C.
Dr. Jack Basman, Charleston, W. Va.
Dr. Franklin A. Benes, Shaker Heights, Ohio
Dr. Arthur P. Black, El Paso, Texas
Dr. William W. Briant, Jr., Pittsburgh, Pa.
Dr. Hugh A. Carithers, Jacksonville, Fla.
Dr. Sims A. Chapman, New Orleans, La.
Dr. E. H. Christopherson, San Diego, Calif.
Dr. Enos Paul Cook, San Jose, Calif.
Dr. Robert J. Cooper, Pontiac, Mich.
Dr. Paul C. Crone, Cleveland, Ohio

Dr. Joseph H. Davis, Palo Alto, Calif.
Dr. Harry F. Dietrich, Beverly Hills, Calif.
Dr. George D. Doroshow, South Gate, Calif.
Dr. R. Cannon Eley, Boston, Mass.
Dr. L. M. Epstein, El Paso, Texas
Dr. Geoffrey W. Esty, Westfield, N. J.
Dr. Merrill W. Everhart, Dallas, Texas
Dr. Herman W. Farber, Petersburg, Va.
Dr. Warren C. Fargo, Cleveland, Ohio
Dr. Clarence Dixon Fowler, Atlanta, Ga.
Dr. Stanley S. Freedman, Providence, R. I.
Dr. Leo S. Friedman, Cincinnati, Ohio
Dr. Harvey F. Garrison, Jr., Jackson, Miss.
Dr. Eugene Gettleman, Sherman Oaks, Calif.
Dr. Ernest L. Glasscock, Kansas City, Mo.
Dr. John K. Glen, Houston, Texas
Dr. Moe Goldstein, Forest Hills, L. I., N. Y.
Dr. Milton M. Greenberg, Washington, D. C.
Dr. Leo Grossman, Miami Beach, Fla.
Dr. Daniel C. Hackett, Rochester, N. Y.
Dr. Salmon R. Halpern, Dallas, Texas
Dr. Albert S. Harden, Jr., Maplewood, N. J.
Dr. Paul Harper, Bridgeport, Conn.
Dr. Joyce I. Hartman, Cleveland, Ohio
Dr. Anna Luvern Hays, Tulsa, Okla.
Dr. George Heller, Englewood, N. J.
Dr. A. Morgan Hill, Grand Rapids, Mich.
Dr. Lewis Webb Hill, Boston, Mass.
Dr. F. Read Hopkins, Lynchburg, Va.
Dr. William A. Howard, Washington, D. C.
Dr. James G. Hughes, Memphis, Tenn.
Dr. Martin J. Hurst, Hollywood, Calif.
Dr. Benjamin M. Kagan, Richmond, Va.
Dr. Joseph M. Klein, Wilkes-Barre, Pa.
Dr. George S. Littell, Plainview, Texas
Dr. Russell W. Mapes, Beverly Hills, Calif.
Dr. Herman B. Marks, Pawtucket, R. I.
Dr. John Walker Maroney, Wilmington, Del.
Dr. R. J. Martoccio, Utica, N. Y.
Dr. R. A. McGuigan, Evanston, Ill.
Dr. John C. McKittrick, Burlington, Iowa
Dr. Henry S. Meyer, Houston, Texas
Dr. John Fleek Miller, Newark, Ohio
Dr. Stephen Dow Mills, Westfield, N. J.
Dr. John McKenney Mitchell, Rosemont, Pa.
Dr. H. J. Morrison, Savannah, Ga.
Dr. Paul N. Morrow, Omaha, Neb.
Dr. Samuel J. Nichamin, Detroit, Mich.
Dr. Ernest L. Noone, Drexel Hill, Pa.
Dr. Edward T. O'Donnell, Wilmington, Del.
Dr. Owen S. Ogden, Louisville, Ky.
Dr. Alfred W. Pinkerton, Lima, Ohio
Dr. Harold D. Pyle, South Bend, Ind.
Dr. William A. Reilly, San Francisco, Calif.
Dr. Harold E. Roe, Pomona, Calif.

Dr. H. A. Rosenberg, Waterbury, Conn.
Dr. Herman Schneck, New York, N. Y.
Dr. Joseph Schwartzman, Brooklyn, N. Y.
Dr. Charles Lee Shafer, Mansfield, Ohio
Dr. John J. Shields, 7500 Brookfield Road, Philadelphia, Pa.
Dr. H. Herman Shuman, Springfield, Mass.
Dr. Carl E. Sibilsky, Peoria, Ill.
Dr. Henry Siegel, Detroit, Mich.
Dr. Walter J. Siemsen, Kalamazoo, Mich.
Dr. Irving Silverman, Roxbury, Mass.
Dr. Lendon Snedeker, Boston, Mass.
Dr. George E. Stafford, Lincoln, Neb.
Dr. Albert F. Stein, Chicago, Ill.
Dr. Neil C. Stone, Poughkeepsie, N. Y.
Dr. Vincent G. Tosti, Ridgewood, Queens, N. Y.
Dr. Alfred A. Trivilino, Jamaica, N. Y.
Dr. James H. Wallace, Oak Park, Ill.
Dr. Charles E. Ward, Jackson, Miss.
Dr. Thomas S. Weaver, Nashville, Tenn.
Dr. George H. Wegmann, Milwaukee, Wis.
Dr. Robert L. Wilder, Minneapolis, Minn.
Dr. R. E. Williams, Chicago, Ill.
Dr. Sherl J. Winter, Dayton, Ohio
Dr. Irving J. Wolman, Philadelphia, Pa.
Dr. J. Andreas Wunderlich, Jr., Pittsburgh, Pa.

Book Reviews

Your Child From One to Six. Children's Bureau Publication 30, U. S. Department of Labor, Washington, D. C., 1945, 146 pages. (May be obtained from the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C.) Price 15 cents.

This 1945 revision of *Child Care—The Preschool Age*, which was first published in 1918 and has had several earlier revisions, is the soundest and safest book in print to place in the hands of the average mother with a young child. It has been carefully written and the text reviewed by a number of outstanding pediatricians, child psychologists, and psychiatrists. The text is closely in keeping with modern thought and is free from the didactic rigidity which marred the earlier editions. The authors in a remarkable way have put technical thought and procedures into good simple English which does not need a glossary or dictionary to be understood. It should and will have a tremendous circulation as every doctor can recommend it to the parents of young children. The authors and Children's Bureau are to be congratulated on having produced such an excellent book on child care and training.

B. S. V.

Men Without Guns. The Story of Army Medicine. Text by DeWitt Mackenzie. Illustrated with 137 plates (118 in color), from the Abbott Collection by Contemporary Artists, Philadelphia, 1945, The Blakiston Company. Price $5.00.

Not only the medical profession, but also the people of the United States are indebted to the Abbott Laboratories for making possible this remarkable graphic presentation of the work of the Medical Corps of the Army in World War II. The idea originated with Lieutenant Colonel Howard Baer, M. A. C., who worked with another Howard Baer, the artist, and Reeves Lowenthal of the Associated Artists, who has done so much to make art available to the rank and file of America. This group interested the Abbott Laboratories in sponsoring the project. With the approval of Surgeon General Kirk, who writes a foreword for the book, a group of outstanding contemporary artists were selected and sent to all the corners of the earth to sketch and paint the work of the Medical Corps.

Many have seen selections from the paintings which have been exhibited in Art Museums in a number of cities and many doctors have carefully put aside in their portfolios the reproductions which have been appearing in recent months in the monthly bulletin of the Abbott Laboratories. Now a selection has been brought together in the volume with an excellent text by DeWitt Mackenzie, war analyst of the Associated Press. While many of the sketches, as would be expected from the nature of the project, are "journalese" in character, not a few in their composition, feeling, and execution rank as works of art which make them stand by themselves. Among them might be mentioned "Anopheles Home Front" and "Night Duty" by Franklin Boggs; "Just Off the Line" and "Men With God" by Robert Benny; "Return Cargo" and "Fireside Comfort" by Lawrence Beal Smith; "Pack Train in China" and the jungle pictures by Howard Baer; "Night Shift" and "Italian Rush Hour" by Joseph Hirsch. The format of the book and printing are excellent, but the color reproductions for some reason or another are not as good as the reproductions in the Abbott Laboratories bulletins.

The collection is now the property of the United States Government. Certainly this vivid portrait of the work of the Medical Corps is a thing which every doctor can look to with pride. A young veteran of New Guinea, Leyte, and Okinawa who returned from Japan a few days before Christmas summed it up. He picked up the book from my desk and quietly looked at the pictures. All he said as he closed it was, "God, those medical guys did a swell job."

B. S. V.

Journal of the History of Medicine and Applied Science. Published quarterly by Henry Schuman. New York.

The appearance of a new journal in medical literature is always a matter of interest, and worthy of examination and note. When a new journal in the history of medicine is issued, special recognition must be given. Such is the case with this new Journal which made its appearance in January, 1946. It is edited by Dr. George Rosen with an able and representative group serving on the editorial board and as consulting editors, the latter group including representatives of many foreign countries and many persons in this country whose names are familiar in the field of the history of medicine.

As stated in the introductory article by the Editor, there is only one other publication in this field in this country, the Bulletin of the History of Medicine. The new Journal will supplement the Bulletin and provide another focus for studies in medical history. Contributions on all aspects of the history of medicine, public health, dentistry, nursing, pharmacy, veterinary medicine, and the various sciences that impinge on medicine will be published. Papers dealing with limited and specific subjects will be supplemented by occasional articles of wider scope that summarize certain important fields and outline the broad trends in them. Several review articles by competent investigators are contemplated.

The first number contains ten original articles of a wide range of interest. There is also a section entitled Notes and Queries, and an abundant section on Book Reviews including those of historical interest.

The publisher is Mr. Henry Schuman of New York, long known to students of medical history and to collectors of medical publications of historical interest. His own personal interest in this field will insure proper guidance for the Journal. It is unusual to find a publisher and an editorial staff with such close common interest. A small amount of appropriate advertising appears in the back section.

The form of the first issue as an example of the Journal is satisfying. Laid paper is used which carries printing and illustrations to good advantage. Half-tone cuts are used for inserts. The over-all appearance and effect are pleasing. The printing is done by a well-known firm recognized for high quality of printing standards.

The Editor states several reasons for the decision to issue another publication in medical history. It may be added that during these times when everybody feels that great progress is being made in civilization and in education, science and allied fields, it is helpful occasionally to pause to consider how much is real progress and how much is only change and rearrangement of ideas and feelings. When one pauses, so to speak, to catch breath and look around, it is necessary always to look backward. It has long been recognized that history moves in cycles. New facts are constantly added, but human thinking and utilization of those facts may not always be a forward movement. It is fortunate then, that such publications as this Journal help to bring the hindsight to our perspective and to make the past part of the prologue.

H. M.

In the Doctor's Office. Esther Jane Parsons, Philadelphia, 1945, J. B. Lippincott Company, 295 pages. Price $2.00.

This is a small book packed full of sound principles and philosophy, useful facts and information, advice and caution and satisfaction. It is good reading for the doctor to see where his responsibilities and difficulties lie and probably what he can do to make the machinery run more smoothly and efficiently in his office. He will surely profit by reading the contents carefully. There is always a new viewpoint or new ideas in such books, and this one is full of such. It is unusually easy to read.

H. M.